PATENT COOPERATION TREATY

Express Mail No. EL662089097US

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Bannerman,David Gardner
WITHERS & ROGERS
Goldings House
2 Hays Lane
London SE1 2HW
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	23.11.2000
Applicant's or agent's file reference DGB/KB503PCT/DE	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB99/02084	23/12/1999	24/12/1998

Applicant
KARO BIO AB et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

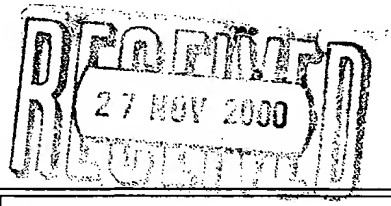
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.



Name and mailing address of the IPEA/

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

Ambroa, J.R.

Tel.+49 89 2399-8012

Form PCT/IPEA/416 (July 1992)

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ _____

Express Mail No. EL662089097US

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: DGB/KB503PCT/DE

International application No.	International filing date *(day month year)*	(Earliest) Priority date *(day month year)*
PCT/IB99/02084	23.12.1999	24.12.1998

Title of invention: NOVEL THYROID RECEPTOR LIGANDS AND METHOD II

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

KARO BIO AB
Novum, S-141 57
Huddinge
Sweden

Telephone No.: +46 8 608 60 46
Facsimile No.: +46 8 774 82 61
Teleprinter No.:

State *(that is, country)* of nationality: Sweden
State *(that is, country)* of residence: Sweden

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

HANGELAND, Jon
234 Louise Drive
Morrisville, PA 19067
U S A

State *(that is, country)* of nationality: USA
State *(that is, country)* of residence: USA

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

ZHANG, Minsheng
31 Scheurman Terrace
Warren, NJ 07059
U S A

State *(that is, country)* of nationality: CHINA
State *(that is, country)* of residence: USA

[X] Further applicants are indicated on a continuation sheet.

See Notes to the demand form

International application No.
PCT/IB99/02084

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name: for a legal entity: full official designation. The address must include postal code and name of country.)*

CARINGAL, Yolanda
24 Coral Tree Ct.
Lawrenceville, NJ 08648
U S A

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
USA	USA

Name and address: *(Family name followed by given name: for a legal entity: full official designation. The address must include postal code and name of country.)*

RYONO, Denis
28 Marion Road West
Princeton, NJ 08540
USA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
USA	USA

Name and address: *(Family name followed by given name: for a legal entity: full official designation. The address must include postal code and name of country.)*

LI, Yi-Lin
Kallbrinksvagen 38C
S-141 31 Huddinge
Sweden

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
CHINA	SWEDEN

Name and address: *(Family name followed by given name: for a legal entity: full official designation. The address must include postal code and name of country.)*

MALM, Johan
Korsangarvagen 53
S-142 40 Skogas
Sweden

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
SWEDEN	SWEDEN

[X] Further applicants are indicated on another continuation sheet.

International application No.
PCT/IB99/02084

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

LIU, Ye
Smedvagen 23
S-146 36
Tullinge
Sweden

State *(that is, country)* of nationality: CHINA

State *(that is, country)* of residence: SWEDEN

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

GARG, Neeraj
Barkvagen 15
S-147 52
Sweden

State *(that is, country)* of nationality: INDIA

State *(that is, country)* of residence: SWEDEN

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

LITTEN, Chris
Stubbestigen 6
S-147 52
Tumba
Sweden

State *(that is, country)* of nationality: INDIA

State *(that is, country)* of residence: SWEDEN

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

GARCÍA COLLAZO, Ana Maria
Moregatan 10
S-118 27
Stockholm
Sweden

State *(that is, country)* of nationality: SPAIN

State *(that is, country)* of residence: SWEDEN

[X] Further applicants are indicated on another continuation sheet.

See Notes to the demand form

International application No.
PCT/IB99/02084

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity: full official designation. The address must include postal code and name of country.)*

KOEHLER, Konrad
Visatravagen 27
S-141 50
Huddinge
Sweden

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
USA	SWEDEN

Name and address: *(Family name followed by given name; for a legal entity: full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity: full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity: full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on another continuation sheet.

International application No.
PCT/IB99/02084

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is [X] agent [ ] common representative

and [X] has been appointed earlier and represents the applicant(s) also for international preliminary examination.

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BANNERMAN, David Gardner
WITHERS & ROGERS
Goldings House
2 Hays Lane
London SE1 2HW
United Kingdom

Telephone No.: +44 1926 336111

Facsimile No.: +44 1926 335519

Teleprinter No.:

[ ] **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special addr ess to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination **to start on the basis of:**

[X] the international application as originally filed

the description
[ ] as originally filed
[ ] as amended under Article 34

the claims
[ ] as originally filed
[ ] as amended under Article 19 (together with any accompanying statement)
[ ] as amended under Article 34

the drawings
[ ] as originally filed
[ ] as amended under Article 34

2. [ ] The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. [ ] The applicant wishes the start of the international preliminary examination **to be postponed** until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: ENGLISH

[X] which is the language in which the international application was filed.
[ ] which is the language of a translation furnished for the purposes of international search.
[ ] which is the language of publication of the international application.
[ ] which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby **elects all eligible States** *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes **not to elect:**

International application No.
PCT/IB99/02084

Box No. VI CHECK LIST

The demand is accompanied by the following elements. in the language referred to in Box No. IV. for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or. where required. translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or. where required. translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☐ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number. if any:
4. ☐ statement explaining lack of signature
5. ☐ nucleotide and or amino acid sequence listing in computer readable form
6. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature. indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

D G BANNERMAN
European Patent Attorney

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5. below. does not apply. ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date. the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

PCT

CHAPTER II

FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

International application No. PCT/IB99/02084	For International Preliminary Examining Authority use only
Applicant's or agent's file reference DGB/KB503PCT/DE	Date stamp of the IPEA
Applicant: KARO BIO AB	

Calculation of prescribed fees

1. Preliminary examination fee ..... [ ] P

2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)* ..... [ ] H

3. Total of prescribed fees
Add the amounts entered at P and H and enter total in the TOTAL box ..... [ ] TOTAL

Mode of Payment

- [ ] authorization to charge deposit account with the IPEA (see below)
- [ ] cheque
- [ ] postal money order
- [ ] bank draft
- [ ] cash
- [ ] revenue stamps
- [ ] coupons
- [ ] other *(specify)*:

Deposit Account Authorization *(this mode of payment may not be available at all IPEAs)*

The IPEA/ _____ [ ] is hereby authorized to charge the total fees indicated above to my deposit account.

[ ] *(this check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

Deposit Account Number _____ Date *(day/month/year)* _____ Signature _____

See Notes to the fee calculation sheet

PATENT COOPERATION TREATY

Express Mail No. EL662089097US

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
WITHERS & ROGERS
Attn. Bannerman,David Gardner
Goldings House
2 Hays Lane
London SE1 2HW
UNITED KINGDOM

Applicant's or agent's file reference DGB/PCT-137	Date of mailing *(day/month/year)* 28/06/2000 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/IB 99/02084	International filing date *(day/month/year)* 23/12/1999
Applicant KARO BIO AB et al.	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Chantal Meyer

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
DGB/PCT-137		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB 99/02084	23/12/1999	24/12/1998
Applicant		
KARO BIO AB et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of Invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   THYROID RECEPTOR LIGANDS

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

BANNERMAN, David, Gardner
Withers & Rogers
Goldings House
2 Hays Lane
London SE1 2HW
ROYAUME-UNI

Date of mailing (day/month/year) 03 February 2000 (03.02.00)	
Applicant's or agent's file reference DGB/PCT-137	**IMPORTANT NOTIFICATION**
International application No. PCT/IB99/02084	International filing date (day/month/year) 23 December 1999 (23.12.99)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 24 December 1998 (24.12.98)
Applicant KARO BIO AB et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
24 Dece 1998 (24.12.98)	9828442.5	GB	17 Janu 2000 (17.01.00)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

I. Britel

Telephone No. (41-22) 338.83.38

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated in the Notification of Receipt of Record Copy (Form PCT/IB/301) by paying national fees and furnishing translations, as prescribed by the applicable national laws.

The time limit for performing these procedural acts is **20 MONTHS** from the priority date or, for those designated States which the applicant elects in a demand for international preliminary examination or in a later election, **30 MONTHS** from the priority date, provided that the election is made before the expiration of 19 months from the priority date. Some designated (or elected) Offices have fixed time limits which expire even later than 20 or 30 months from the priority date. In other Offices an extension of time or grace period, in some cases upon payment of an additional fee, is available.

In addition to these procedural acts, the applicant may also have to comply with other special requirements applicable in certain Offices. **It is the applicant's responsibility** to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most designated Offices do not issue reminders to applicants in connection with the entry into the national phase.

For detailed information about the procedural acts to be performed to enter the national phase before each designated Office, the applicable time limits and possible extensions of time or grace periods, and any other requirements, see the relevant Chapters of Volume II of the PCT Applicant's Guide. Information about the requirements for filing a demand for international preliminary examination is set out in Chapter IX of Volume I of the PCT Applicant's Guide.

GR and ES became bound by PCT Chapter II on 7 September 1996 and 6 September 1997, respectively, and may, therefore, be elected in a demand or a later election filed on or after 7 September 1996 and 6 September 1997, respectively, regardless of the filing date of the international application. (See second paragraph above.)

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date. If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with an indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity to furnish the priority document within a time limit which is reasonable under the circumstances.

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit is the filing date of the earliest application whose priority is claimed.

PATENT COOPERATION TREATY

Express Mail No. EL662089097US

From the INTERNATIONAL BUREAU

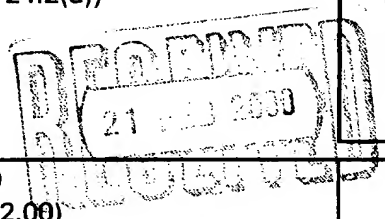
PCT

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))

To:

BANNERMAN, David, Gardner
Withers & Rogers
Goldings House
2 Hays Lane
London SE1 2HW
ROYAUME-UNI



Date of mailing (day/month/year)	IMPORTANT NOTIFICATION
03 February 2000 (03.02.00)	
Applicant's or agent's file reference	**International application No.**
DGB/PCT-137	PCT/IB99/02084

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

KARO BIO AB (for all designated States except US)
HANGELAND, Jon et al (for US)

International filing date	:	23 December 1999 (23.12.99)
Priority date(s) claimed	:	24 December 1998 (24.12.98)
Date of receipt of the record copy by the International Bureau	:	17 January 2000 (17.01.00)
List of designated Offices	:	

AP :GH,GM,KE,LS,MW,SD,SL,SZ,TZ,UG,ZW
EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
OA :BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
National :AE,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,NO,NZ,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,US,UZ,VN,YU,ZA,ZW

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- [X] time limits for entry into the national phase
- [ ] confirmation of precautionary designations
- [ ] requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

I. Britel

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

BANNERMAN, David, Gardner
Withers & Rogers
Goldings House
2 Hays Lane
London SE1 2HW
ROYAUME-UNI

Date of mailing (day/month/year)
27 March 2001 (27.03.01)

Applicant's or agent's file reference
DGB/PCT-137

IMPORTANT NOTIFICATION

International application No.
PCT/IB99/02084

International filing date (day/month/year)
23 December 1999 (23.12.99)

1. The following indications appeared on record concerning:
[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address

State of Nationality | State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:
[X] the person [X] the name [X] the address [X] the nationality [X] the residence

Name and Address
BRISTOL-MYERS SQUIBB COMPANY
P.O. Box 4000
Princeton, NJ 08543-4000
United States of America

State of Nationality: US | State of Residence: US

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:
Additional applicant for all designated states except US.

4. A copy of this notification has been sent to:
[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
I. Britel
Telephone No.: (41-22) 338.83.38

PCT

Express Mail No. EL662089095

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* DGB/PCT-137

Box No. I TITLE OF INVENTION

NOVEL THYROID RECEPTOR LIGANDS AND METHOD II

Box No. II APPLICANT

Name and address: *(Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

KARO BIO AB
Novum, S-141 57
Huddinge
SWEDEN

☐ This person is also inventor.

Telephone No. +46 8 608 60 46

Facsimile No. +46 8 774 82 61

Teleprinter No.

State *(that is, country)* of nationality: SWEDEN

State *(that is, country)* of residence: SWEDEN

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

HANGELAND, Jon
234 Louise Drive
Morrisville, PA 19067
USA

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: USA

State *(that is, country)* of residence: USA

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country.)*

BANNERMAN, David Gardner
WITHERS & ROGERS
Goldings House
2 Hays Lane
London SE1 2HW
United Kingdom

Telephone No. + 44 1926 336111

Facsimile No. +44 1926 335519

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ZHANG, Minsheng
31 Scheurman Terrace
Warren, NJ 07059
USA

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: CHINA

State *(that is, country)* of residence: USA

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

CARINGAL, Yolanda
24 Coral Tree Ct
Lawrenceville, NJ 08648
USA

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: USA

State *(that is, country)* of residence: USA

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

RYONO, Denis
28 Marion Road West
Princeton, NJ 08540
USA

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: USA

State *(that is, country)* of residence: USA

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name: for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

LI, Yi-Lin
Kallbrinksvagen 38C
S-141 31 Huddinge
Sweden

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: CHINA

State *(that is, country)* of residence: SE

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

[X] Further applicants and/or (further) inventors are indicated on another continuation sheet.

FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

MALM, Johan
Korsangarvagen 53,
S-142 40 Skogas
Sweden

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: SE

State *(that is, country)* of residence: SE

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

LIU, Ye
Smedvagen 23
S-146 36
Tullinge
Sweden

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: CHINA

State *(that is, country)* of residence: SE

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

GARG, Neeraj
Barkvagen 15
S-147 52
Sweden

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: INDIA

State *(that is, country)* of residence: SE

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

LITTEN, Chris
Stubbestigen 6
S-147 52
Tumba
Sweden

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: INDIA

State *(that is, country)* of residence: SE

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

[X] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the follo[redacted] sub-boxes is used, this sheet should not be [redacted]uded in the request.

Name and address: *(Family name follo[redacted]by given name; for a legal entity, full official designation. The address must include [redacted] code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

GARCIA COLLAZO, Ana Maria
Moregatan 10
S-118 27
Stockholm
Sweden

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: ES

State *(that is, country)* of residence: SE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

KOEHLER, Konrad
Visatravägen 27
S-141 50
Huddinge
Sweden

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: USA

State *(that is, country)* of residence: SE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- ☒ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☒ **AE** United Arab Emirates
- ☒ **AL** Albania .....
- ☒ **AM** Armenia .....
- ☒ **AT** Austria .....
- ☒ **AU** Australia .....
- ☒ **AZ** Azerbaijan
- ☒ **BA** Bosnia and Herzegovina .....
- ☒ **BB** Barbados
- ☒ **BG** Bulgaria .....
- ☒ **BR** Brazil .....
- ☒ **BY** Belarus .....
- ☒ **CA** Canada
- ☒ **CH and LI** Switzerland and Liechtenstein
- ☒ **CN** China .....
- ☒ **CU** Cuba .....
- ☒ **CZ** Czech Republic .....
- ☒ **DE** Germany .....
- ☒ **DK** Denmark .....
- ☒ **EE** Estonia .....
- ☒ **ES** Spain .....
- ☒ **FI** Finland .....
- ☒ **GB** United Kingdom
- ☒ **GD** Grenada
- ☒ **GE** Georgia .....
- ☒ **GH** Ghana .....
- ☒ **GM** Gambia
- ☒ **HR** Croatia .....
- ☒ **HU** Hungary .....
- ☒ **ID** Indonesia
- ☒ **IL** Israel .....
- ☒ **IN** India .....
- ☒ **IS** Iceland
- ☒ **JP** Japan .....
- ☒ **KE** Kenya .....
- ☒ **KG** Kyrgyzstan .....
- ☒ **KP** Democratic People's Republic of Korea .....
- ☒ **KR** Republic of Korea .....
- ☒ **KZ** Kazakhstan .....
- ☒ **LC** Saint Lucia
- ☒ **LK** Sri Lanka
- ☒ **LR** Liberia
- ☒ **LS** Lesotho .....
- ☒ **LT** Lithuania
- ☒ **LU** Luxembourg
- ☒ **LV** Latvia
- ☒ **MD** Republic of Moldova .....
- ☒ **MG** Madagascar .....
- ☒ **MK** The former Yugoslav Republic of Macedonia .....
- ☒ **MN** Mongolia
- ☒ **MW** Malawi .....
- ☒ **MX** Mexico .....
- ☒ **NO** Norway
- ☒ **NZ** New Zealand .....
- ☒ **PL** Poland .....
- ☒ **PT** Portugal .....
- ☒ **RO** Romania
- ☒ **RU** Russian Federation .....
- ☒ **SD** Sudan
- ☒ **SE** Sweden
- ☒ **SG** Singapore
- ☒ **SI** Slovenia .....
- ☒ **SK** Slovakia .....
- ☒ **SL** Sierra Leone .....
- ☒ **TJ** Tajikistan .....
- ☒ **TM** Turkmenistan .....
- ☒ **TR** Turkey .....
- ☒ **TT** Trinidad and Tobago .....
- ☒ **UA** Ukraine .....
- ☒ **UG** Uganda .....
- ☒ **US** United States of America .....
- ☒ **UZ** Uzbekistan .....
- ☒ **VN** Viet Nam .....
- ☒ **YU** Yugoslavia .....
- ☒ **ZA** South Africa .....
- ☒ **ZW** Zimbabwe .....

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

- ☐ .....
- ☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	When earlier application is: national application: country	regional application:* Regional Office	international application: receiving Office
item (1) 24/12/1998	9828442.5	GB		
item (2)				
item (3)				

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): _____

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*: ISA /

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*: Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST: LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	:	7
description (excluding sequence listing part)	:	46
claims	:	12
abstract	:	1
drawings	:	
sequence listing part of description	:	
Total number of sheets	:	67

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☒ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

Figure of the drawings which should accompany the abstract:

Language of filing of the international application:

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

D. G. Bannerman

22nd December 1999

For receiving Office use only

1. Date of actual receipt of the purported international application:
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

*1. If, in any of the Boxes, **the space is insufficient** to furnish all the information: in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:*

*(i) **if more than two persons are involved as applicants and/or inventors** and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below:*

*(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication **"the States indicated in the Supplemental Box"** is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant:*

*(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, **the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America**: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor:*

*(iv) if, in addition to the agent(s) indicated in Box No. IV, there are **further agents**: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV:*

*(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "**patent of addition**," or "**certificate of addition**," or if, in Box No. V, the name of the United States of America is accompanied by an indication "**continuation**" or "**continuation-in-part**": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application:*

*(vi) if, in Box No. VI, there are **more than three earlier applications whose priority is claimed**: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI:*

*(vii) if, in Box No. VI, **the earlier application is an ARIPO application**: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed.*

*2. If, with regard to the **precautionary designation statement** contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.*

*3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning **non-prejudicial disclosures or exceptions to lack of novelty**: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.*

Continuation of Box IV

D.G. Bannerman
N.M. Wilson
W.M. Blatchford
M. Adkins
A.J. Chettle
J.P. Dean

I. S. Harison
D.M. Pratt
B.J.N. Dempster
K.J. Barnfather
S.A. Beck
P.C. Turner
H.H.B. Wright

D. Croston
D.C. Jones
J.B. Jones

of

WITHERS & ROGERS
GOLDINGS HOUSE
2 HAYS LANE
LONDON SE1 2HW
GB

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET

Annex to the Request

Receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's file reference: DGB/PCT-137

Applicant: KARO BIO AB

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . 55 [T]

2. SEARCH FEE . . . . . 638 [S]

International search to be carried out by _____

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains 59 sheets.

first 30 sheets . . . . . 285 [b1]

21 remaining sheets x 6 additional amount = 126 [b2]

Add amounts entered at b1 and b2 and enter total at B . . . . 411 [B]

Designation Fees

The international application contains 79 designations.

10 number of designation fees payable *(maximum 10)* x 65 amount of designation fee = 650 [D]

Add amounts entered at B and D and enter total at I . . . . . 1061 [I]

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT *(if applicable)* . . . . . [P]

5. TOTAL FEES PAYABLE . . . . . 1754 TOTAL

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

☐ authorization to charge deposit account (see below)
☐ bank draft
☐ coupons
☐ cheque
☐ cash
☐ other *(specify)*:
☐ postal money order
☐ revenue stamps

DEPOSIT ACCOUNT AUTHORIZATION *(this mode of payment may not be available at all receiving Offices)*

The RO/ _____

☐ is hereby authorized to charge the total fees indicated above to my deposit account.

☐ *(this check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

☐ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

Deposit Account No. _____ Date *(day/month/year)* _____ Signature _____

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
DGB/PCT-137		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB 99/02084	23/12/1999	24/12/1998
Applicant		
KARO BIO AB et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   THYROID RECEPTOR LIGANDS

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

PATENT COOPERATION TREATY

RECD 27 NOV 2000
WIPO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
DGB/KB503PCT/DE		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB99/02084	23/12/1999	24/12/1998
International Patent Classification (IPC) or national classification and IPC		
C07D257/04		
Applicant		
KARO BIO AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22/04/2000	23.11.2000
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Von Daacke, A Telephone No. +49 89 2399 8286

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB99/02084

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-46 as originally filed

Claims, No.:

1-29 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

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(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 23,24,28,29 (Ind. Applicability).

because:

☒ the said international application, or the said claims Nos. 23,24,28,29 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3,4,7-12,15-22
	No:	Claims	1,2,5,6,13,14,23-29
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-29
Industrial applicability (IA)	Yes:	Claims	1-22,25-27

No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

III NON-ESTABLISHMENT

Claims 23,24,28 and 29 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

V REASONED STATEMENT

1. PRIOR ART

The documents cited in the International Search Report
D1: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US STN, CAPLUS accession no. 1971:540431, XP002139408 -& CHEMICAL ABSTRACTS, vol. 75, no. 23, 6 December 1971 (1971-12-06) Columbus, Ohio, US; abstract no. 140431, XP002139407 & K. MASUDA ET AL: TAKEDA KENKYUSHO HO, vol. 29, no. 4, 1970, pages 545-552,
D2: WO 96 40048 A (KARO BIO AB) 19 December 1996 (1996-12-19)
D3: DE 32 31 541 A (HENNING BERLIN GMBH) 1 March 1984 (1984-03-01)
D4: M. ANDRE ET AL: J. CHROMATOGR. A, vol. 725, no. 2, 1996, pages 287-294, XP004039616
D5: M. ADAMCZYK ET AL: BIOCONJUGATE CHEM., vol. 8, no. 2, 1997, pages 133-145, XP000906993
D6: US-A-4 741 897 (J. ANDREWS ET AL) 3 May 1988 (1988-05-03)
D7: EP-A-0 580 550 (CIBA-GEIGY AG) 26 January 1994 (1994-01-26)

have been considered for the examination procedure.

2. NOVELTY

The subject-matter of Claims 1,2,5,613,14 and 23-29 is anticipated by D1-D6 Article 33(2) PCT). All documents disclose single compounds or compound

groups (D6) which are covered by the present mentioned claims.
It is noted that more compounds as mentioned in the Search Report are novelty destroying, e.g.D4 compound II and D5 compounds 26 and 27.
The compounds according to the remaining claims appear however not disclosed in the cited prior art.

3. INVENTIVE STEP

The claimed subject-matter does not fulfil the requirements of Article 33(3) PCT for the following reasons.

The closest state of the art for the present application is equally represented by the cited documents as they relate all to thyrosin derivatives. D7 discloses structurally similar thyromimetic compounds which do not fall under the present application because of the C=O-Z substitution, only. Various corresponding substituents which are used in the present compounds are, however known from D1-D6. A man skilled in the art, aware of the disclosure of D1-D6 on the one hand and that of D7 on the other hand, would have arrived at the corresponding present compounds without further inventive ingenuity and obviously expected the same qualitative properties shown by the prior art compounds.
Therefore, the problem underlying the present application should be seen in the provision of new thyrosin derivatives having unexpected properties over those of the closest prior art compounds. In the absence of comparative test results or other appropriate information it is not possible to decide whether such a problem has been solved or not. In the case where comparative tests are envisaged in order to support an inventive step, these must be carried out between the compounds of the present application having the maximum structural similarity with the compounds of the closest prior art, such that the effect is shown to have its origins in the distinguishing feature of the claimed invention.
The definitions of R_4 and R^1 are speculative as the terms 'substituted', heteroaromatic', 'heteroaryl' and 'amino acid' without further specification are open definitions for which the alleged activity can hardly be demonstrated. All those variants which are in principle known from the prior art or may be regarded as reasonable generalisation of the exemplified ones are acceptable under Art. 33(3) PCT.

4. INDUSTRIAL APPLICABILITY

No objection for Claims 1-22, 25, 26 and 27. For the assessment of the other claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VI CERTAIN DOCUMENTS CITED

D8: M. EBISAWA ET AL: CHEM. PHARM. BULL., vol. 47, no. 9, 1999, pages 1348-1350, XP000906992

This document discloses single compounds coverd by present Claim 1. The priority documents have not been checked re Article 33(3) PCT.

VIII CERTAIN OBSERVATIONS (CLAIMS)

1. Claim 1 does not include the definitions R' and R".

2. The reason for the proviso at the end of Claim 1 is unclear.

3. The term 'prodrug' does not satisfy Art. 5 PCT. One of the basic prodrug requirements is to be seen in its reconversion to the parent drug in vivo. This prodrug-drug conversion may take place before absorption, during absorption, after absorption or at the specific side of drug action in the body, all dependent upon the specific goal for which the prodrug is designed whereby the prodrug **per se** is inactive. The description is, however, completely silent as to what kind of prodrugs are contemplated with the claimed invention, e.g. which inactive functional derivatives are able or at least believed to be able to convert into a final

drug. The term 'prodrug' can also not be accepted under Art. 6 PCT.
The term is to be seen as a functional feature. Functional features are, however, allowable only if the result is one which can be directly and positively verified by tests or procedures adequately specified in the description or known to a person skilled in the art and which do not require undue experimentation. At page 8, a reference has been inserted to "The practice of Medicinal Chemistry (and the references contained therein). This more generic disclosure does not appear to be an 'adequately specification in the description'.

4. The reference back to Claim 1 made in Claim 26 is incorrect.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07C 311/00

A2

(11) International Publication Number: WO 00/39077

(43) International Publication Date: 6 July 2000 (06.07.00)

(21) International Application Number: PCT/IB99/02084

(22) International Filing Date: 23 December 1999 (23.12.99)

(30) Priority Data:
9828442.5 24 December 1998 (24.12.98) GB

(71) Applicant *(for all designated States except US)*: KARO BIO AB [SE/SE]; Novum, S–141 57 Huddinge (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: HANGELAND, Jon [US/US]; 234 Louise Drive, Morrisville, PA 19067 (US). ZHANG, Minsheng [CN/US]; 31 Scheurman Terrace, Warren, NJ 07059 (US). CARINGAL, Yolanda [US/US]; 24 Coral Tree Court, Lawrenceville, NJ 08648 (US). RYONO, Denis [US/US]; 28 Marion Road West, Princeton, NJ 08540 (US). LI, Yi–Lin [CN/SE]; Kallbrinksvagen 38C, S–141 31 Huddinge (SE). MALM, Johan [SE/SE]; Korsangarvagen 53, S–142 40 Skogas (SE). LIU, Ye [CN/SE]; Smedvagen 23, S–146 36 Tullinge (SE). GARG, Neeraj [IN/SE]; Barkvägen 15, S–147 52 Tumba (SE). LITTEN, Chris [IN/SE]; Stubbestigen 6, S–147 52 Tumba (SE). GARCIA COLLAZO, Ana Maria [ES/SE]; Moregatan 10, S–118 27 Stockholm (SE). KOEHLER, Konrad [US/SE]; Visatravagen 27, S–141 50 Huddinge (SE).

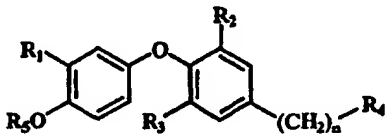
(74) Agents: BANNERMAN, David, Gardner et al.; Withers & Rogers, Goldings House, 2 Hays Lane, London SE1 2HW (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: NOVEL THYROID RECEPTOR LIGANDS AND METHOD II



(I)

(57) Abstract

New thyroid receptor ligands are provided which have general formula (I) in which: n is an integer from 0 to 4; R_1 is halogen, trifluoromethyl, or alkyl of 1 to 6 carbons or cycloalkyl of 3 to 7 carbons; R_2 and R_3 are the same or different and are hydrogen, halogen, alkyl of 1 to 4 carbons or cycloalkyl of 3 to 5 carbons, at least one of R_2 and R_3 being other than hydrogen; R_4 is a carboxylic acid amide (CONR'R'') or an acylsulphonamide (CONHSO2R') derivative, or a pharmaceutically acceptable salt thereof, and all stereoisomers thereof; or when n is equal to or greater than one, R_4 may be a heteroaromatic moiety which may be substituted or unsubstituted, or an amine (NR'R''). R_5 is hydrogen or an acyl (such as acetyl or benzoyl) or other group capable of bioconversion to generate the free phenol structure (wherein R_5=H). In addition, a method is provided for preventing, inhibiting or treating a disease associated with metabolism dysfunction or which is dependent upon the expression of a T_3 regulated gene, wherein a compound as described above is administered in a therapeutically effective amount. Examples of such diseases associated with metabolism dysfunction or are dependent upon the expression of a T_3 regulated gene include obesity, hypercholesterolemia, atherosclerosis, cardiac arrhythmias, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer as well as glaucoma, congestive heart failure and skin disorders.

NOVEL THYROID RECEPTOR LIGANDS AND METHOD II

Field of the Invention

This invention relates to novel compounds which are thyroid receptor ligands, and are preferably selective for the thyroid hormone receptor β, to methods of preparing such compounds and to methods for using such compounds such as in the regulation of metabolism.

Background of the Invention

While the extensive role of thyroid hormones in regulating metabolism in humans is well recognized, the discovery and development of new specific drugs for improving the treatment of hyperthyroidism and hypothyroidism has been slow. This has also limited the development of thyroid hormone agonists and antagonists for treatment of other important clinical indications, such as hypercholesterolemia, obesity and cardiac arrhythmias.

Thyroid hormones affect the metabolism of virtually every cell of the body. At normal levels, these hormones maintain body weight, the metabolic rate, body temperature, and mood, and influence serum low density lipoprotein (LDL) levels. Thus, in hypothyroidism there is weight gain, high levels of LDL cholesterol, and depression. In excess with hyperthyroidism, these hormones lead to weight loss, hypermetabolism, lowering of serum LDL levels, cardiac arrhythmias, heart failure, muscle weakness, bone loss in postmenopausal women, and anxiety.

Thyroid hormones are currently used primarily as replacement therapy for patients with hypothyroidism. Therapy with L-thyroxine returns metabolic functions to normal and can easily be monitored with routine serum measurements of levels of thyroid-stimulating hormone (TSH), thyroxine (3,5,3',5'-tetraiodo-L-thyronine, or T_4) and triiodothyronine (3,5,3'-triiodo-L-thyronine, or T_3). However, replacement therapy, particularly in older individuals is limited by certain of the deleterious effects of thyroid hormones.

In addition, some effects of thyroid hormones may be therapeutically useful in non-thyroid disorders if adverse effects can be minimized or eliminated. These potentially useful influences include weight reduction, lowering of serum LDL levels, amelioration of depression and stimulation of bone formation. Prior attempts to utilize thyroid hormones pharmacologically to treat these disorders have been limited by manifestations of hyperthyroidism, and in particular by cardiovascular toxicity.

Development of specific and selective thyroid hormone receptor agonists could lead to specific therapies for these common disorders while avoiding the cardiovascular and other toxicities of native thyroid hormones. Tissue-selective thyroid hormone agonists may be obtained by selective tissue uptake or extrusion, topical or local delivery, targeting to cells through other ligands attached to the agonist and targeting receptor subtypes. Thyroid

hormone receptor agonists that interact selectively with the β-form of the thyroid hormone receptor offers an especially attractive method for avoiding cardio-toxicity.

Thyroid hormone receptors (TRs) are, like other nuclear receptors, single polypeptide chains. The various receptor forms appear to be products of two different genes α and β. Further isoform differences are due to the fact that differential RNA processing results in at least two isoforms from each gene. The $TR\alpha_1$, $TR\beta_1$ and $TR\beta_2$ isoforms bind thyroid hormone and act as ligand-regulated transcription factors. In adults, the $TR\beta_1$ isoform is the most prevalent form in most tissues, especially in the liver and muscle. The $TR\alpha_2$ isoform is prevalent in the pituitary and other parts of the central nervous system, does not bind thyroid hormones, and acts in many contexts as a transcriptional repressor. The $TR\alpha_1$ isoform is also widely distributed, although its levels are generally lower than those of the $TR\beta_1$ isoform. This isoform may be especially important for development. Whereas many mutations in the TRβ gene have been found and lead to the syndrome of generalized resistance to thyroid hormone, mutations leading to impaired TRα function have not been found.

A growing body of data suggest that many or most effects of thyroid hormones on the heart, and in particular on the heart rate and rhythm, are mediated through the α-form of the TRα1 isoform, whereas most actions of the hormone such as on the liver, muscle and other tissues are mediated more through the β-forms of the receptor. Thus, a TRβ-selective agonist might not elicit the cardiac rhythm and rate influences of the hormones but would elicit many other actions of the hormones. It is believed that the α-form of the receptor is the major drive to heart rate for the following reasons:

1) tachycardia is very common in the syndrome of generalized resistance to thyroid hormone in which there are defective TRβ-forms, and high circulating levels of T_4 and T_3;

2) there was a tachycardia in the only described patient with a double deletion of the TRβ gene (Takeda et al, J. Clin. Endrocrinol. & Metab. 1992, Vol. 74, p. 49);

3) a double knockout TRα gene (but not β-gene) in the mouse has a slower pulse than control mice; and,

4) western blot analysis of human myocardial TRs show presence of the $TR\alpha_1$, $TR\alpha_2$ and $TR\beta_2$ proteins, but not $TR\beta_1$.

If these indications are correct, then a TRβ-selective agonist could be used to mimic a number of thyroid hormone actions, while having a lesser effect on the heart. Such a compound may be used for: (1) replacement therapy in elderly subjects with hypothyroidism who are at risk for cardiovascular complications; (2) replacement therapy in elderly subjects with subclinical hypothyroidism who are at risk for cardiovascular complications; (3) obesity; (4) hypercholesterolemia due to

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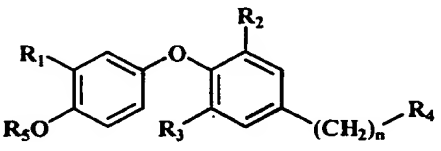
elevations of plasma LDL levels; (5) depression; and, (6) osteoporosis in combination with a bone resorption inhibitor.

Description of the Invention

In accordance with the present invention, compounds are provided which are thyroid receptor ligands, and have the general formula I:

I



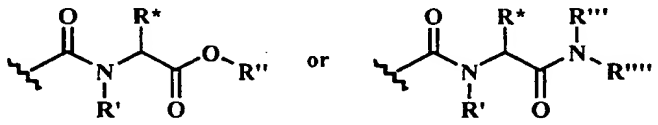
in which:

n is an integer from 0 to 4;

R_1 is halogen, trifluoromethyl, or alkyl of 1 to 6 carbons or cycloalkyl of 3 to 7 carbons;

R_2 and R_3 are the same or different and are hydrogen, halogen, alkyl of 1 to 4 carbons or cycloalkyl of 3 to 5 carbons, at least one of R_2 and R_3 being other than hydrogen;

R_4 is a heteroaromatic moiety which may be substituted or unsubstituted and is linked to $(CH_2)_n$ via a nitrogen atom or a carbon atom; an amine (NR'R"), including those in which the amine is derived from an alpha amino acid of either natural (L) or unnatural (D) stereochemistry; an acylsulphonamide ($CONHSO_2R'$) or a carboxylic acid amide (CONR'R'') in which the amine portion of the carboxylic amide can be derived from an achiral or a L or D alpha amino acid such as when the general structure -CONR'R'' can be represented by



and R', R'', R''' and R'''' are the same or different and are independently selected from hydrogen, alkyl, aryl and heteroaryl, substituted or unsubstituted, and R* may be hydrogen, alkyl, aryl and heteroaryl, substituted or unsubstituted, and may also be any of the side chains found in the naturally occuring alpha-amino acids and their analogs, including those examples wherein R' and R* are connected to form 4 to 8-membered rings (such as when R' and R* comprise consecutive $-(CH_2)-$ groups to form proline or homoproline); and with the proviso that when n equals zero (n = 0), then R_4 can only be a carboxylic acid amide or an acylsulphonamide.

R_5 is hydrogen or an acyl (such as acetyl or benzoyl) or other group capable of bioconversion to generate the free phenol structure (wherein R_5 = H);

including all stereoisomers thereof, prodrug esters thereof, and pharmaceutically acceptable salts thereof.

In addition, in accordance with the present invention, a method for preventing, inhibiting or treating a disease associated with metabolism dysfunction or which is dependent upon the expression of a T_3 regulated gene is provided, wherein a compound of formula I is administered in a therapeutically effective amount. The compound of formula I is preferably an agonist that is preferably selective for the thyroid hormone receptor-beta. Examples of such diseases associated with metabolism dysfunction or are dependent upon the expression of a T_3 regulated gene are set out hereinafter and include obesity, hypercholesterolemia, atherosclerosis, cardiac arrhythmias, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer as well as glaucoma and congestive heart failure.

Detailed Description of the Invention

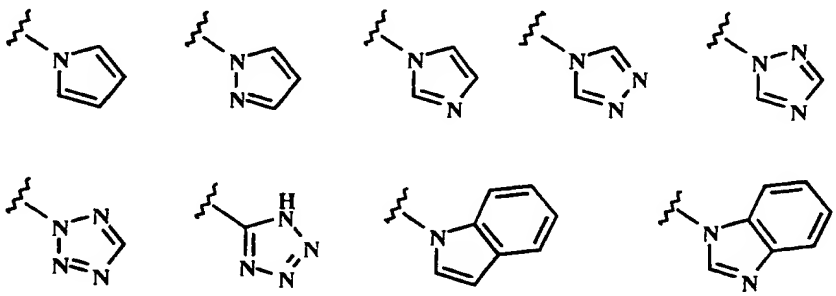
The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

The term "thyroid receptor ligand" as used herein is intended to cover any moiety which binds to a thyroid receptor. The ligand may act as an agonist, an antagonist, a partial agonist or a partial antagonist.

The term "aliphatic hydrocarbon(s) as used herein refers to acyclic straight or branched chain groups which include alkyl, alkenyl or alkynyl groups.

The term "aromatic hydrocarbon(s) as used herein refers to groups including aryl groups as defined herein.

The term "heteroaryl" or "heteroaromatic moiety" as used herein alone or as a part of another group refers to a 5- or 6-membered aromatic ring which includes 1, 2, 3, or 4 heteroatoms, one of which must be a nitrogen atom; the other heteroatoms when present may be nitrogen, oxygen or sulfur, and such rings may be fused to another aryl or heteroaryl ring, and includes possible N-oxides. The heteroaryl group may optionally include 1 to 4 substituents such as aryl, alkyl, alkenyl, alkynyl, cycloalkyl, hydroxy, cyano, nitro, amino and/or carboxyl, and including the following



and the like.

Unless otherwise indicated, the term "lower alkyl", "alkyl" or "alk" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 12 carbons (in the case of alkyl or alk), in the normal chain, preferably 1 to 4 carbons, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, or isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, which may be optionally substituted with 1 to 4 substituents which may include alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, hydroxy, cyano, nitro, amino and/or carboxyl.

The term "aryl" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl including 1-naphthyl and 2-naphthyl) and may be optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, hydroxy, amino, nitro, cyano and carboxylic acids.

Unless otherwise indicated, the term "lower alkenyl" or "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 12 carbons, preferably 2 to 5 carbons, in the normal chain, which include one to six double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, and the like, which may be substituted as in the case of "alkyl".

Unless otherwise indicated, the term "lower alkynyl" or "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 12 carbons, preferably 2 to 8 carbons, in the normal chain, which include one triple bond in the normal chain, such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonynyl, 4-decynyl,3-undecynyl, 4-dodecynyl and the like, which may be substituted as in the case of "alkyl".

Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated cyclic hydrocarbon groups or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups, containing one ring and a total of 3 to 7 carbons, preferably 3 to 5 carbons, forming the ring, which includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl and cyclohexenyl, , which may be substituted as in the case of "alkyl".

The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine as well as CF_3, with chlorine or bromine being preferred.

The compounds of formula I can be present as salts, in particular pharmaceutically acceptable salts. If the compounds of formula I have, for example, at least one basic center, they can form acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms which are unsubstituted or substituted, for example, by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, (for example aspartic or glutamic acid or lysine or arginine), or benzoic acid, or with organic sulfonic acids, such as (C_1-C_4) alkyl or arylsulfonic acids which are unsubstituted or substituted, for example by halogen, for example methyl- or *p*-toluene- sulfonic acid. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds of formula I having at least one acid group (for example COOH) can also form salts with bases. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono, di or trilower alkylamine, for example ethyl, tertbutyl, diethyl, diisopropyl, triethyl, tributyl or dimethyl-propylamine, or a mono, di or trihydroxy lower alkylamine, for example mono, di or triethanolamine. Corresponding internal salts may furthermore be formed. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds I or their pharmaceutically acceptable salts, are also included.

Preferred salts of the compounds of formula I which include a basic groups include monohydrochloride, hydrogensulfate, methanesulfonate, phosphate or nitrate.

Preferred salts of the compounds of formula I which include an acid group include sodium, potassium and magnesium salts and pharmaceutically acceptable organic amines.

Preferred are compounds of the invention of formula I wherein R_1 is isopropyl;

R_2 and R_3 are independently halogen such as bromo or chloro; or

R_2 and R_3 are each methyl or one is methyl and the other is ethyl;

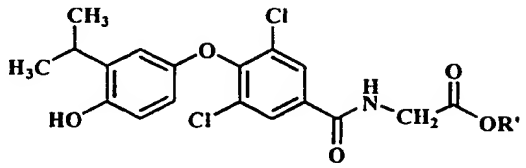
or one of R_2 and R_3 is halogen such as bromo or chloro, and the other is alkyl such as methyl, or hydrogen; and

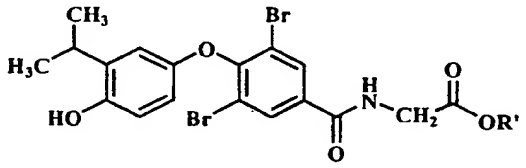
n is 0, 1 or 2;

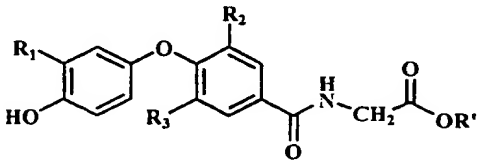
R_4 is carboxylic acid derivative of the type: amides, acylsulphonamides or an amide formed from an amino acid residue; and

R_5 is hydrogen.

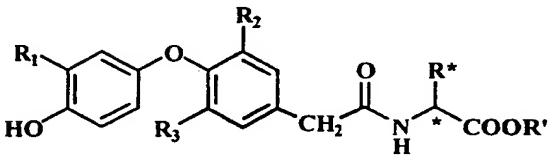
The most preferred compounds have the structures:



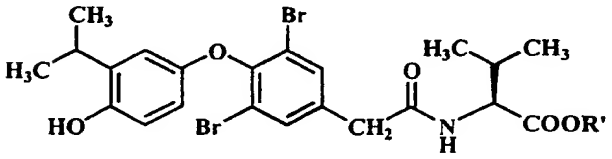


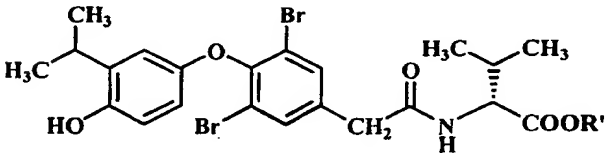


and other preferred compounds of the invention have the structures:



for example





wherein R_1 = isopropyl, methyl, ethyl, tertiary-butyl, cyclopentyl, cyclohexyl; R_2 and R_3 may be independently selected from Br, Cl and Me; R* may be hydrogen, alkyl, cycloalkyl, aryl and heteroaryl; * denotes either D or L stereochemistry; and R' and is selected from hydrogen, lower alkyl, especially ethyl and methyl or where the group COOR' represents prodrug ester forms known in the art such as pivaloyloxymethyl or

dioxolenylmethyl. Such prodrug esters are described in standard references such as Chapter 31, written by Camille G. Wermuth et al., in "The Practice of Medicinal Chemistry", ed. C. G. Wermuth. Academic Press, 1996 (and the references contained therein).

The compounds of formula I may be prepared by the exemplary processes described in the following reaction schemes. Exemplary reagents and procedures for these reactions appear hereinafter and in the working Examples.

Compounds of formula I of the invention can be prepared using the sequence of steps outlined in Schemes 1 to 5 set out below.

Scheme 1 depicts a synthesis of compounds of formula I in which R_4 = an amino acid, aniline derivative or aza containing heterocyclic ring, which through their nitrogen atom is connected to the aromatic ring by an intervening $(CH_2)_n$ group.

In Scheme 1, the amino acid, aniline derivative or aza containing heterocyclic ring, dissolved in a suitable solvent, is treated with 1-3 molar equivalents of an appropriate base, such as potassium carbonate, cesium carbonate, potassium hydroxide or sodium hydride. The resulting anion is then alkylated with the substituted iodide 5. Other combinations of alkylating agents or bases may be employed and are known to those skilled in the art. The reaction mixture is stirred at room temperature or heated until the starting materials are consumed. After standard work-up and purification, the methyl ether function is removed by treatment with 3-6 molar equivalents of a strong acid such as boron tribromide at 0°C to 25°C in an inert solvent such as dichloromethane. The reaction mixture gives after standard work-up and purification, the end products 6. Numerous alternative methodologies for the conversion of intermediates such as 3 and 4 to products 6 are well known to those skilled in the art.

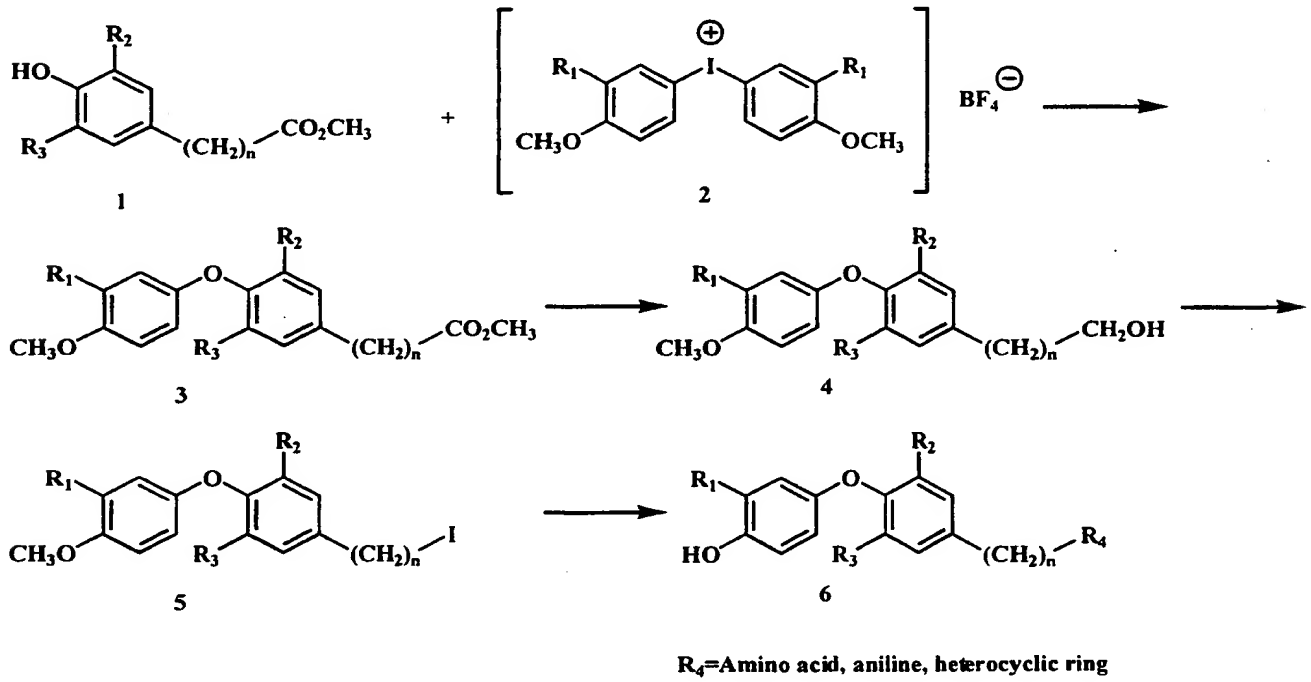
Scheme 1 also outlines the preparation of the intermediate iodide 5, the sequence similar to what is employed in: "Novel Thyroid Receptor Ligands and Methods. Li, Yi-Lin; Liu, Ye; Hedfors, Asa; Malm, Johan; Mellin, Charlotta; Zhang, Minsheng. PCT Int. Appl., 40 pp. CODEN: PIXXD2. WO 9900353 A1 990107". An anisole-derived iodonium salt 2 and copper bronze in an inert solvent such as dichloromethane are mixed at room temperature. A mixture of the appropriate phenol ester 1 and a base such as triethylamine in an inert solvent such as dichloromethane was added to the mixture, generally using 2 molar equivalents each of the phenol and base, and 3 molar equivalents of iodonium salt 2. After stirring overnight at room temperature, the reaction mixture is purified via chromatography on silica gel, to give biaryl ether products 3. Other methods exist in the literature for the synthesis of diaryl ethers, for example, two references directly apply to the synthesis of thyroid hormone analogs: D. A. Evans et al., Tet. Letters, volume 39, 2937-2940 (1998) and G. M. Salamonczyk et al., Tet. Letters, volume 38, 6965-6968 (1997). The carboxylic acid ester can be hydrolyzed with a mixture of aqueous sodium hydroxide and methanol. The methyl ether function can be removed by treatment of the free acid product of the previous procedure with 4-6 molar

equivalents of a strong acid such as boron tribromide at 0°C in an inert solvent such as dichloromethane. Other combinations of protecting groups for the carboxylic acid present in 1 and phenolic hydroxyl in iodonium salt 2 can be employed, and their usage is known to those skilled in the art (references describing protecting group strategy include, for example, "Protecting Groups in Organic Chemistry", J. F. W. McOmie, Plenum Press, London, New York, 1973, and "Protective Groups in Organic Synthesis", T. W. Greene, Wiley, New York, 1984).

The intermediate ester product 3 is reduced by treatment with an appropriate reducing agent such as diisobutyl aluminium hydride in an inert solvent such as tetrahydrofuran at 0°C. If R_2 and R_3 are alkyl, then lithium aluminum hydride may be employed without the risk of reducing away halogen substituents at those positions. Standard work-up and purification yields the desired alcohol product 4. Other reducing agents may be employed and are known to those skilled in the art.

Intermediate 4 in Scheme 1 is finally converted to the intermediate iodide 5 by treatment of alcohol 4 with 2 molar quivalents of sodium iodide, phosphorous pentaoxide and phosphorous acid, and heated at 120°C for 15 minutes. Numerous other methodologies for conversion of simple hydroxyl groups to the corresponding alkyl iodides are well known to those skilled in the art.

Scheme 1

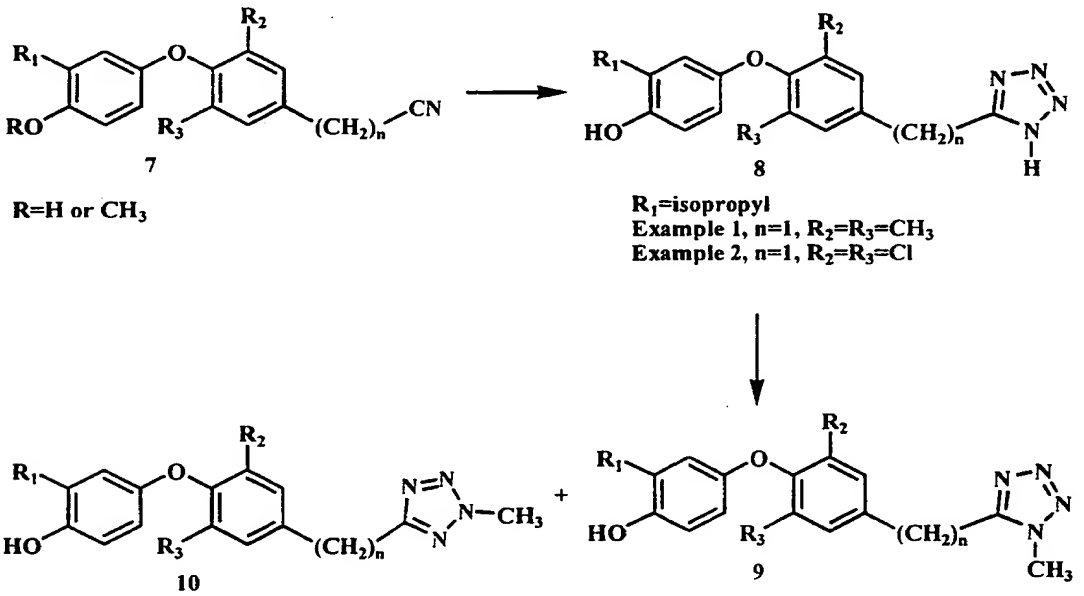


R_4=Amino acid, aniline, heterocyclic ring

Scheme 2 depicts a synthesis of compounds of formula I in which R_4 is a tetrazole ring. Phenylacetonitrile 7 is readily prepared from benzylic iodide 5 by standard means such as reaction with sodium cyanide in a solvent mixture such as water/ethanol. Reaction of phenylacetonitrile 7, with sodium azide and ammonium chloride in dimethylformamide at elevated temperatures gives tetrazole derivatives 8 (Example 1 and 2), after standard work-up and purification procedures. In Example 2 this step was followed by a standard demethylation procedure, as above, in order to remove the protecting group.

Examples of substituted tetrazoles that can be prepared by further chemistry are also depicted in Scheme 2. Tetrazole derivative 8 can for instance be treated with an appropriate base such as sodium hydrogen carbonate in acetone, followed by N-alkylation with methyl iodide to afford derivatives 9 and 10, after standard work-up and purification procedures. Other alkylating agents and bases may be employed and are known to those skilled in the art.

Scheme 2



Examples of compounds of formula I in which R_4 is an amide produced by coupling to an amino acid are shown in Scheme 3. The following procedures all involve the coupling of benzoic or acetic acid derivative 11 (n= 0 or 1), with its phenolic hydroxyl group either protected by a methyl, left unprotected or bound to a resin, with various protected amino acids, to afford the corresponding amides 10 of 3,5-dihalo-4-(4-hydroxy-3-isopropyl-phenoxy) carboxylic acids. The carboxylic acids 11 are readily obtained, for example, by hydrolysis of the corresponding esters 3.

In one procedure, a mixture of 11 with R=Me, a coupling reagent such as 3-ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI), and a base such as 1-hydroxybenzotriazole hydrate (HBT) in dichloromethane is stirred at room temperature. The appropriate protected amino acid and N-methylmorpholine is added. The reaction mixture yields after work-up and purification by either chromatography or recrystallization the corresponding coupled material, which after standard demethylation and hydrolysis procedures, gives the desired final amide products (Example 87).

Several examples of coupled products, employing different protecting groups for the carboxylic acid group was also prepared and isolated (Examples 29, 57, 71-72, 75, 77, 80-82, 84). Alternatively, amide end-products which contain free carboxylic acid groups can be re-esterified by standard procedures by, for instance, heating them in a mixture of refluxing methanol and thionyl chloride, to give the corresponding alkyl acid ester derivatives (Example 82).

In another more fruitful modification of the same procedure as above, 11 is kept unprotected (R=H) from the beginning of the sequence to give, after basic hydrolysis or treatment with a Lewis acid as BBr_3, and standard work-up and purification procedures, other examples of carboxylic acid amides (Example 3-24, 25-28, 56, 73-74, 76, 78-79, 83, 85-86, 203, 207-208).

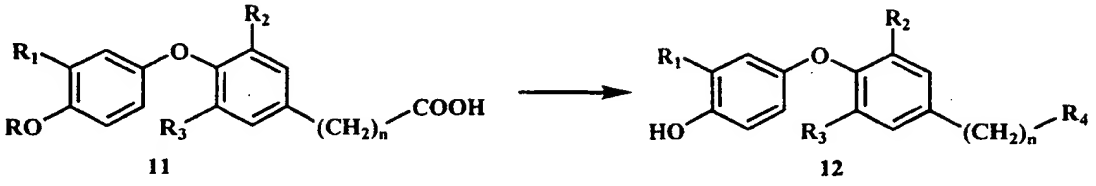
An amide library can also be prepared by solid phase synthesis (Examples 30-55). In this procedure a methyl ester of intermediate 11 is loaded on a resin such as a Merrifield resin by standard procedures, well known to those skilled in the art. The resulting resin is then treated with sodium hydroxide in methanol to provide the resin-bond free carboxylic acid form of 11. Each resin pin is then filled with a solution of the corresponding aminoacid ester, PyBOP (benzotriazole-1-yl-oxy-tris-pyrrolidino phosphonium hexafluorophosphate), HBT, and N,N-diisopropylethylamine (Hunig's base, DIEA) and an inert solvent such as dichloromethane and is stirred at room temperature for days. Other combinations of base and coupling reagents can be employed here with successful results. After treatment of each of the individual pins with an appropriate base such as aqueous potassium hydroxide and washing of the resin, the amides are disassembled from the resin by treatment of a mixture of trifluoroacetic acid, dimethylsulfite and water.

Several other related methodologies exist for the coupling of amino acids with aromatic, as well as non-aromatic, carboxylic acids in solution or solid phase and are known to those skilled in the art.

The amino acid product 12 can reduced by treatment with an appropriate reagent such as sodium borohydride in an polar solvent such as ethanol at room temperature. If R_2 and R_3 are alkyl, then lithium aluminum hydride may be employed without the risk of reducing the halogen substituents at those positions. Standard work-up and purification yields the

desired alcohol product. Other reducing agents may be employed and are known to those skilled in the art.

Scheme 3



11

R= Me, H or resin

12

R_1=isopropyl, R_4=C(=O)—Amino acid

Example 30-55, 207, n=0, R_2=R_3=Br
Example 3-24, 25-28, 56, 73, 76, 78-79, 83, 85, n=1, R_2=R_3=Br
Example 74, n=1, R_2=R_3=Cl
Example 86-87, 203, 208, n=0, R_2=R_3=Cl

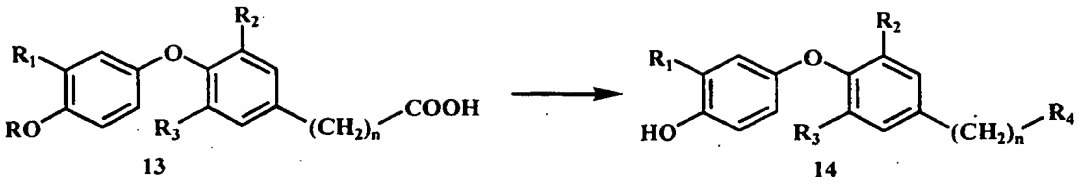
Scheme 4 depicts a synthesis of compounds of formula I in which R_4 is an acylsulphonamide. Similar procedures as for the coupling of amino acids above are employed.

In one procedure, 13 is kept unprotected (R=H), mixed with a base such as DIEA and the appropriate sulphonamide in dichloromethane. Dimethylformamide is added to the mixture if the sulphonamide does not dissolve completely. Treatment of the mixture with a base and coupling reagent combinations such as HOBt and PyBOP, gives after heating and subsequent mild acid treatment during work-up and purification by HPLC, the desired acylsulphonamides (Example 58-70).

In an exemplified procedure, a mixture of 13 with R=Me, a coupling reagent such as 3-ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI), and a base such as dimethylaminopyridine (DMAP) and the appropriate sulphonamide in dichloromethane is stirred at room temperature. The reaction mixture yields after work-up and purification by either chromatography or recrystallization the corresponding coupled material, which after standard demethylation procedures, yields yet other acylsulphonamides.

Other combinations of protecting groups and procedures can be employed. For example, applying similar chemistry as above , but with R= $Si(CH_3)_2t$-Bu, gives further examples of acylsulphonamides after removal of the protecting silyl group with ammonium fluoride (Examples 88-91).

Scheme 4



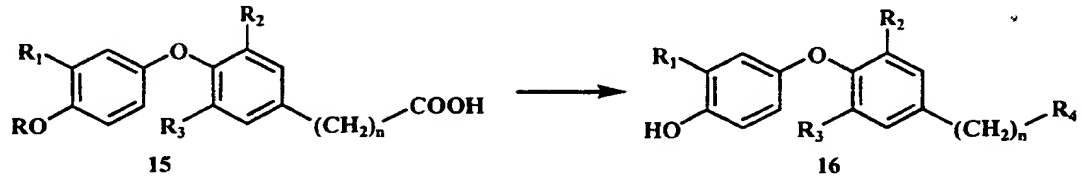
The procedures described in Scheme 5 further exemplify methods for the synthesis of compounds of formula I. Several structurally diverse amides, primary as well as secondary, were prepared as outlined in Scheme 5. Many alternative procedures for the coupling of amino acids above can be employed and are well known to those skilled in the art.

For example, in one procedure secondary diacetic acids amides are obtained through the treatment of 15 by dimethyliminodiacetate and EDCI in dimethylformamide or dichloromethane, followed by standard work-up procedures and final basic hydrolysis of the ester function (Example 206).

In another procedure, aromatic amides were obtained by a similar procedure as in Example 3-24 above (Example 192-202).

A library comprising 100 diverse primary and secondary amides was also prepared in an automated fashion, using standard literature methods (Example 92-191).

Scheme 5



With respect to the above reaction schemes, although the various R_1, R_2, R_3, R_4 and n moieties are specifically defined, unless otherwise indicated, it is to be understood that R_1, R_2, R_3, and R_4 may be any of the groups encompassed thereby and n may be 0, 1, 2, 3 or 4.

The compounds of the invention are agonist that are preferably selective for the thyroid hormone receptor-beta, and as such are useful in the treatment of obesity, hypercholesterolemia and atherosclerosis by lowering of serum LDL levels, alone or in combination with a lipid modulating drug such as an HMG-CoA reductase inhibitor, fibrate, thiazolidinedione, or MTP inhibitor, amelioration of depression alone or in combination with an antidepressant, and stimulation of bone formation to treat osteoporosis in combination with any known bone resorption inhibitor such as alendronate sodium. In addition, the compounds of the invention may be useful as replacement therapy in elderly patients with hypothyroidism or subclinical hypothyroidism who are at risk of cardiovascular complications, in the treatment of the elderly to provide a sense of well-being, and in the treatment of non-toxic goiter; in the management of papillary or follicular thyroid cancer (alone or with T_4); in the treatment of skin disorders such as psoriasis, glaucoma, cardiovascular disease such as in the prevention or treatment of atherosclerosis, and congestive heart failure.

The compounds of the invention may also be used to treat skin disorders or diseases involving dermal atrophy such as glucocorticoid induced dermal atrophy, including restoration of dermal atrophy induced by topical glucocorticoids, the prevention of dermal atrophy induced by topical glucocorticoids (such as the simultaneous treatment with topical glucocorticoid or a pharmacological product including both glucocorticoid and a compound of the invention), the restoration/prevention of dermal atrophy induced by systemic treatment with glucocorticoids, restoration/prevention of atrophy in the respiratory system induced by local treatment with glucocorticoids, UV-induced dermal atrophy, or dermal atrophy induced by aging (wrinkles, etc.), wound healing, keloids, stria, cellulite, roughened skin, actinic skin damage, lichen planus, ichtyosis, acne, psoriasis, Dernier's disease, eczema, atopic dermatitis, chloracne, pityriasis and skin scarring.

In treating skin disorders or diseases as described above, the compounds of the invention may be used in combination with a retinoid or a vitamin D analog.

The compounds of the invention can be administered orally or parenterally such as subcutaneously or intravenously, as well as by nasal application, rectally or sublingually to various mammalian species known to be subject to such maladies, e.g., humans, cats, dogs and the like in an effective amount within the dosage range of about 0.1 to about 100 mg/kg, preferably about 0.2 to about 50 mg/kg and more preferably about 0.5 to about 25 mg/kg (or from about 1 to about 2500 mg, preferably from about 5 to about 2000 mg) on a regimen in single or 2 to 4 divided daily doses.

The active substance can be utilized in a composition such as tablet, capsule, ointment, hydrophilic ointment, cream, lotion, solution or suspension or in other types of carrier of materials such as transdermal devices, iontophoretic devices, rectal suppositories, inhalant devices and the like. The composition or carrier will contain about 5 to about 500

mg per unit of dosage of a compound of formula I. They may be compounded in conventional matter with a physiologically acceptable vehicle or carrier, excipient, binder, preservative, stabilizer, flavor, etc., as called for by accepted pharmaceutical practice.

The following working Examples represent preferred embodiments of the present invention. Appropriate procedures for the preparation of starting materials can be found in: "Novel Thyroid Receptor Ligands and Methods. Li, Yi-Lin; Liu, Ye; Hedfors, Asa; Malm, Johan; Mellin, Charlotta; Zhang, Minsheng. PCT Int. Appl., 40 pp. CODEN: PIXXD2. WO 9900353 A1 990107". The ^{1}H NMR spectra was all consistent with the assigned structures.

Example 1

3,5-Dimethyl-4-(4-hydroxy-3-isopropylphenoxy)benzyltetrazole.

To a stirred solution of 3,5-dimethyl-4-(4-hydroxy-3-isopropylphenoxy)-phenylacetonitrile (154 mg) in 6.3 ml of dimethyl formamide, ammonium chloride (297 mg, 5.21 mmol) and sodium azide (339 mg, 5.21 mmol) was added at reflux. After 4.5 hours the reaction mixture was concentrated, treated with 6 M hydrochloric acid and extracted several times with ethyl acetate. The combined organic phases were dried over magnesium sulphate, filtered and concentrated. The residue was purified by column chromatography (silica gel, 96:4:1 chloroform/methanol/acetic acid) to give 68 mg (37%) of the title compound.

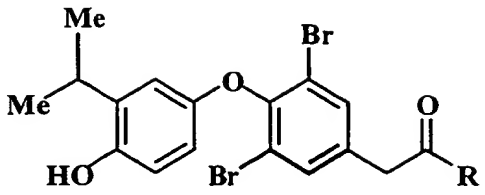
Example 2

3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzyltetrazole.

(a) To a stirred solution of 3,5-dichloro-4-(4-methoxy-3-isopropylphenoxy)-phenylacetonitrile (160 mg) in 3.0 ml of dimethyl formamide, ammonium chloride (500 mg) and sodium azide (600 mg) was added at reflux. After 2 hours the reaction mixture was concentrated, treated with 6 M hydrochloric acid and extracted several times with ethyl acetate. The combined organic phases were dried over magnesium sulphate, filtered and concentrated. The residue was purified by column chromatography (silica gel, 96:4:1 chloroform/methanol/acetic acid) to give 60 mg (34%) of 3,5-dichloro-4-(4-methoxy-3-isopropylphenoxy)benzyltetrazole.

(b) A reaction mixture of 3,5-dichloro-4-(4-methoxy-3-isopropylphenoxy)-benzyltetrazole (60 mg), $BF_3.Me_2S$ (0.5 ml) and CH_2Cl_2 (6 ml) was stirred at room temperature over night. The yield after purification was quantitative.

Examples 3-24

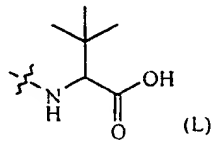
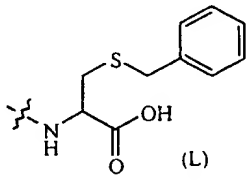
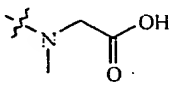
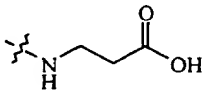
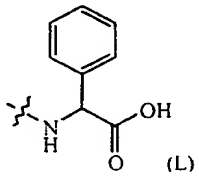
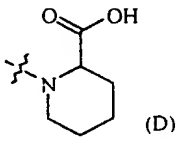
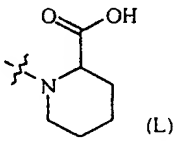


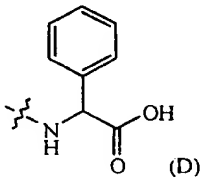
General Procedure

A mixture of 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (222 mg), 3-ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI), (95 mg), 1-hydroxybenzotriazole hydrate (HBT), (91 mg), in dichloromethane (5 ml) was stirred under argon at room temperature for 2 h. In a separate flask, the appropriate amino acid, triethylamine (100 mg) and 5 ml of dichloromethane was stirred for 1 h under N_2. The two mixtures were combined and the reaction mixture stirred at 40C over night. When the starting carboxylic acid was consumed, the organic phase was removed *in vacuo* and the residue dissolved in methanol (20 ml) and 1N NaOH (10 ml). The reaction mixture was stirred at 40C for 24 h and evaporated. The residue was subjected to semi-preparative HPLC, using gradient elution as outlined below. The amine part "R", and the stereochemistry of the aminoacids is indicated in the table below.

[1]HPLC retention time in minutes and gradient method. Reverse phase HPLC analyses performed on Zorbax-C8-5u-4.6x50 mm analytical columns, flow rate 3 ml/min, detection at 220 nm, and a 10 minute gradient elution by solvent A (10 % CH_3CN+10 mmol HOOH) and B (CH_3CN + 10 mmol HOOH). Gradient elution was done in the following way: 0-1 min 90% A, 1-7 min to 100% B, 7-9 min 100% B and 9-10 min return to 10% A. Purification of the Examples were done using a Zorbax-C8-5u-21.5x50 mm semi-preperative column, flow rate 25 ml/min, detection at 220 nm, using the same gradient as for the analytical column.
[2]MS result obtained on a PESciEx API150EX using electrospray, both positive and negative ion modes.

Example	R	Mol Formel	MS m/z (M+H)[1]	HPLC[2]
3	L-Val	C22H25Br2NO5	544.0	6.10
4	L-Val	C22H25Br2NO5	544.0	6.07
5	L-Tyr	C26H25Br2NO6	608.5	5.67

6	 (L)	C23H27Br2NO5	558.1	6.03
7	 (L)	C27H27Br2NO5S	638.2	5.49
8	D-Leu	C23H27Br2NO5	558.1	5.38
9	D-Tyr	C26H25Br2NO6	608.2	5.00
10	D-Trp	C28H26Br2N2O5	631.3	5.38
11	L-Arg	C23H28Br2N4O5	601.3	4.54
12	L-Abu	C21H23Br2NO5	530.2	6.22
13		C20H21Br2NO5	516.1	4.77
14		C20H21Br2NO5	516.1	4.61
15	L-Leu	C23H27Br2NO5	558.1	5.38
16	 (L)	C25H23Br2NO5	578.2	5.23
17	D-Pro	C22H23Br2NO5	542.2	4.92
18	L-Ile	C23H27Br2NO5	558.1	5.38
19	 (D)	C23H25Br2NO5	556.3	5.23
20	L-Phe	C26H25Br2NO5	592.0	5.46
21	L-Lys	C23H28Br2N2O5	573.1	3.77
22	 (L)	C23H25Br2NO5	556.0	5.30
23	L-Pro	C22H23Br2NO5	542.2	4.84

24	 (D)	C25H23Br2NO5	578.2	5.30

Example 25

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]methionine

(a) A solution of 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (222 mg), 3-ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI), (106 mg), 1-hydroxybenzotriazole hydrate (HBT), (101 mg) in dimethyl formamide (5.5 ml) was stirred at room temperature for 0.5 h followed by addition of a solution of *D*-methionine methyl ester hydrochloride (298 mg) and triethylamine (111 mg) in dimethyl formamide (2.2 ml). After stirring for one hour, the mixture was partitioned between water and chloroform. The organic phase was dried, filtered and concentrated. The residue was subjected to column chromatography (Silica gel, gradient elution with 20% to 40% ethyl acetate in petroleum ether), to give 256 mg (87%) of *D*-methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropyl-phenoxy)phenylacetyl] methionate. LC-MS (electrospray): m/z 590 (M+H).

(b) *D*-Methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]-methionate (88 mg) was hydrolyzed by treatment with 1 M aqueous sodium hydroxide (1 ml) in methanol (2.25 ml), to give 81 mg (94%) of the title compound after column chromatography (Silica gel, gradient elution with chloroform, methanol and acetic acid). LC-MS (electrospray): m/z 574 (M-H).

Example 26

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]methionine

(a) 3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (222 mg) was coupled with *D*-methionine hydrochloride (298 mg) using the method described in Example 25(a), to give 236 mg (80%) of *L*-methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropyl-phenoxy)phenylacetyl]methionate after column chromatography. (Silica gel, gradient elution with 20% to 40% ethyl acetate in petroleum ether). LC-MS (electrospray): m/z 590 (M+H).

(b) *D*-Methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropyl-phenoxy)phenylacetyl]-methionate (24 mg) was hydrolyzed using the method described in Example 25(b) to give 20 mg (87%) of the title compound after column chromatography (Silica gel, gradient elution with chloroform, methanol and acetic acid). LC-MS (electrospray): m/z 574 (M-H).

Example 27

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl] α-methylalanine

(a) 3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (222 mg) was coupled with *D*-α-methylalanine hydrochloride (238 mg) using the method described in Example 25(a), to give 269 mg (92%) of *D*-t-butyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl] α-methylalanine after column chromatography (Silica gel, gradient elution with 20% to 40% ethyl acetate in petroleum ether). LC-MS (electrospray): m/z 586 (M+H).

(b) *D*-t-Butyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl] α-methylalanine (88 mg) was was treated with boron tribromide (1 M in dichloromethane, 2.3 ml) at 0°C. The mixture was stirred overnight at room temperature before ice/water was added. The layers were separated and the water layer was extracted with dichloromethane. The combined organic layer was dried, filtered and concentrated, to give 46 mg (58%) of the title compound after column chromatography (Silica gel, gradient elution with chloroform, methanol and acetic acid). LC-MS (electrospray): m/z 528 (M-H).

Example 28

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspargine.

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (444 mg) was mixed with 10 ml thionyl chloride and heated at reflux for 3 h. The reaction mixture was co-evaporated with toluene to give the crude 3,5-dibromo-4-(4-hydroxy-3-isopropyl-phenoxy)phenylacetyl chloride. N,O-bis(trimethylsilyl)acetamide (670 mg) was added at 0 °C, under nitrogen atmosphere, to a mixture of *D*-Aspargine (225 mg) and 10 ml acetonitrile. The reaction mixture was further stirred at room temperature and a solution of 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl chloride in 10 ml acetonitrile was added.

After stirring for 16 h, the reaction mixture was poured into water and the solid filtered off. The solid was dissolved in methanol and the organic phase removed *in vacuo*. The residue was purified by HPLC to give 76 mg (14%) of *D*- N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspargine. LC-MS (electrospray): m/z 557 (M-H).

Example 29

L-Methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]alanine

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (200 mg) was coupled with *L*-methyl alanine hydrochloride (126 mg) using the method described in Example 25(a), to give 140 mg (60%) of the title compound. LC-MS (electrospray): m/z 530 (M+1).

General procedure for the preparation of the amino acid library by solid phase synthesis (Examples 30-55)

Loading of the resin with 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy benzoic acid:

A mixture of methyl 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoate (7.6g, 17.1mmol), Merrifield resin (5g, 1.2mmol/g) and sodium hydride (432 mg, 18 mmol) in 100 ml of dimethyl formamide was stirred in a 250 ml round flask at 50 °C for 40 hours. After cooling, the mixture was filtered and the resin was washed with water (3x 10 ml), dimethyl formamide (3x10 ml), ethyl acetate(3x10 ml) and dichloromethane(3x10 ml). The resulting resin was dried in vacuum overnight to give 8.54g of resin, loaded with the methyl ester.

To the resin was added methanol (100 ml) and an aqueous solution of sodium hydroxide (100 ml, 1M). The suspension was stirred under at 80°C for one day, cooled to room temperature and filtered. The resin was washed with water (3x10 ml), tetrahydrofuran (3x10 ml), ethyl acetate (3x10 ml) and dichloromethane(3x10 ml). After drying under vacuum, 5.94 g of resin loaded with the title compound was obtained.

Determination of the loading capacity of the resin:

The resin (100 mg) was treated with a mixture of trifluoroacetic acid, dimethyl sulphite and water (85:15:5). The mixture was stirred at room temperature for two days. The resin was removed by filtration and the organic phase was collected and concentrated under vacuum. The resulting residue was chromatographed on silica gel (methanol/chloroform/

acetic acid 10:90:1). The pure fractions were pooled and concentrated affording 17.5 mg (51%) of 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoic acid as white solid. The loading rate was estimated as 0.04 mmol (17,5 mg) per 100 mg of loaded resin.

Coupling of 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy) benzoic acid to different amino acids

DIVERSOMER® 8-100 synthesizer was used for syntheses and Savant SpeedVac® system for concentration.

To each of eight PINs was added 100 (±5) mg of the loaded resin (17.5 mg /100 mg; 0.04 mmol/100 mg). The resin-filled PINs were placed in the holder block. Eight vials (12 ml) were placed into the reservoir rack, equipped with a magnetic stir bar and filled with a mixture consisting of the corresponding aminoacid ester (0.4 mmol), PyBOP (104 mg, 0.2 mmol), HBT (27 mg, 0.2 mmol), DIEA (52 mg, 0.4 mmol) and dichloromethane (5 ml). The holder block was assembled with the reservoir rack. The reaction was carried out at room temperature with stirring for two days. The reservoir rack was disassembled from the holder block. Each resin in the PINs was dispended with 2 ml each of dimethyl formamide, water, ethyl acetate and dichloromethane. The washing procedure was repeated twice. The resin in PINs was finally dried by pressed air-flow.

Eight new vials (12 ml) were placed into the reservoir rack and each vial was equipped with a magnetic stir bar. The holder block was assembled with the reservoir rack. A methanolic solution of potassium hydroxide (5 ml, 2 M) was in 1 ml increments down through the inside of each PIN. The apparatus was allowed to stand in a fume hood with stirring for two days. The synthesizer was disassembled and the resins were washed with water (4x2 ml), methanol (4x2 ml) and dichloromethane (4x2 ml). The resin in PINs was dried by pressed air-flow.

The holder block was reassembled from the reservoir rack. A 50 ml stock solution of trifluoroacetic acid/dimethyl sulphite/water(85:15:5; v/v) was prepared. The solution (5 ml) was added to each of the eight PINs in 1 ml increments. The apparatus was allowed to stand in a fume hood with stirring for 2 days. The resercoir rack and the holder block was disassembled. Each PIN was washed with 1 ml of the above solution. The contents of the 8 reservoir vials were concentrated to dryness. Each vial was partitioned between aqueous hydrochloric acid (1 ml, 1 M) and ethyl acetate (2 ml). The content of the eight reservoir vials were carefully transferred into the eight drying cartridges (Chem elute CE1003, VARIAN), equipped with test tubes underneath. The cartridges were allowed to drain by gravity, rinsed with ethyl acetate (3x1.5 ml) after 5 min and finally forced to drain under reduced pressure. The organic layer was collected and concentrated to give the following products in the yields mentioned below.

Example 30

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]valine

12.2mg (57.7%)

Example 31

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]leucine

20.1mg (92.5%)

Example 32

L-S-Benzyl, N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]cysteine

14.9mg(60%)

Example 33

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]tyrosine

5.9mg(24.8%)

Example 34

L-N-δ-(2,2,5,7,8-Pentamethylchroman-6-sulfonyl),
N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]arginine

10.7mg(31%)

Example 35

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aminobutyric acid

15.6 mg (75,5%)

Example 36

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]valine

19.7 mg (93%)

Example 37

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]leucine
14.8 mg (68%)

Example 38

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]proline
8.6 mg (41%)

Example 39

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]cysteine

2.88 mg (13.5%)

Example 40

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]glycine

15.8 mg (81%)

Example 41

L-N-α-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]lysine

23.5 mg (105%)

Example 42

D-N-α-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]lysine

24.9 mg (112%)

Example 43

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aminoisobutyric acid

6.72 mg (32.6%)

Example 44

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]phenylglycine

7.1 mg (31%)

Example 45

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]phenylglycine

15.1 mg (67%)

Example 46

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]sarcosine

6.7 mg (33.4%)

Example 47

DL-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]-α-methylphenylalanine

7.4 mg (31.4%)

Example 48

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]isoleucine

16.1 mg (70%)

Example 49

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]methionine

11.7 mg (52%)

Example 50

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]methionine

13.2 mg (58.6%)

Example 51

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]phenylalanine

9.7 mg (41.9%)

Example 52

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]phenylalanine

12.2 mg (52.9%)

Example 53

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]cyclohexylalanine

10.1mg(43.7%)

Example 54

L-N-ε-(Benzyloxycarbonyl), N-α-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)-benzoyl]lysine

10 mg (36%)

Example 55

D-N-ε-(Benzyloxycarbonyl), N-α-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)-benzoyl]lysine

24.4 mg (88%)

Example 56

L-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]alanine

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (200 mg) was coupled with *L*-methyl alanine hydrochloride (126 mg) using the method described in Example 25(a) and subsequently hydrolyzed using the method described in Example 25(b). The crude mixture was purified by semi-preparative HPLC, to give 40 mg (21%) of *L*-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]alanine. LC-MS (electrospray): m/z 516 (M+H).

Example 57

L-Dimethyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamate

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (200 mg) was coupled with *L*-dimethyl glutamate hydrochloride (190 mg) using the method described in Example 25(a). The crude mixture was purified by semi-preparative HPLC, to give 150 mg (55%) of the title compound. LC-MS (electrospray): m/z 601 (M+1).

Example 58

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-5-hydroxy-1-naphthalenesulphonamide

To a stirred mixture of 5-hydroxy-1-naphthalenesulphonamide (0.175 mmol) in dichloromethane (0.2 ml) was added a solution of 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoic acid (0.035 mmol), DIEA (0.175 mmol) and dichloromethane (0.2 ml). dimethyl formamide was added to the solution if the sulphonamide not dissolved completely in dichloromethane. After 15 minutes PyBOP (0.042 mmol) and HOBt (0.001 mmol) in dichloromethane (0.3 ml) was added. The reaction mixture was heated at 50°C for 20 hours. After cooling to room temperature, dichloromethane (1 ml) and citric acid solution (5%, 1ml) was added and stirred vigorously for 30 min. The organic phase was dried, concentrated and the residue was finally subjected to semi-preparative HPLC (Silica column: 250x20mm, ethyl acetate/n-heptane (both with 0.5% acetic acid). Gradient: first 2min 15% ethyl acetate, then over 13min to 100% ethyl acetate, then additional 5 min 100% ethyl acetate) to give 12 mg (54 %) of the title compound.

Example 59

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-toluenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with toluenesulphonamide (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 14 mg (69 %) of the title compound.

Example 60

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-nitrobenzenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (, 0.035 mmol) was coupled with 4-nitrophenylsulfonamid (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 8 mg (37 %) of the title compound.

Example 61

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl sulfamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with sulfamide (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 13 mg (73 %) of the title compound.

Example 62

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-5-dimethylamino-1-naphthalene-sulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with 5-dimethylamino-1-naphthalenesulphonamide (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 8 mg (34 %) of the title compound.

Example 63

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-aminobenzenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with 4-aminobenzenesulphonamide (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 7 mg (34 %) of the title compound.

Example 64

Methyl-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-2-sulphonamide] benzoate

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with methyl 2-sulphonamide benzoate (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 12 mg (55 %) of the title compound.

Example 65

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-2-aminobenzenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with 2-aminobenzenesulphonamide (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 11 mg (54 %) of the title compound.

Example 66

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-2-toluenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with 2-toluenesulphonamide (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 15 mg (74 %) of the title compound.

Example 67

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-(2-aminoethyl)benzenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with 4-(2-aminoethyl)benzenesulphonamide (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 10 mg (47 %) of the title compound.

Example 68

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-(2-aminomethyl)benzenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (, 0.035 mmol) was coupled with 4-(2-aminomethyl)benzenesulphonamide (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 16 mg (76 %) of the title compound.

Example 69

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-3-nitrobenzenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with 3-nitrobenzenesulphonamide (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 7 mg (33 %) of the title compound.

Example 70

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-chlorobenzenesulphonamide

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (0.035 mmol) was coupled with 4-chlorobenzenesulphonamide (0.175 mmol) using the method described in Example 58. Purification on HPLC of the residue gave 13 mg (62 %) of the title compound.

Example 71

L-Dimethyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamate

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (200 mg) was coupled with *L*-dimethyl glutamate hydrochloride (190 mg) using the method described in Example 25(a). The crude mixture was purified by semi-preparative HPLC, to give 150 mg (55%) of the title compound. LC-MS (electrospray): m/z 601 (M+H).

Example 72

L-(O-*tert*-butyl)methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl] glutamate

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (200 mg) was coupled with *L*-(O-*tert*buthyl)methyl glutamate hydrochloride (228 mg) using the method described in Example 25(a). The crude mixture was purified by semi-preparative HPLC, to give 70 mg (24%) of the title compound. LC-MS (electrospray): m/z 643 (M+H).

Example 73

L-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamic acid

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (200 mg) was coupled with *L*-dimethyl glutamate hydrochloride (190 mg) using the method described in Example 25(a) and subsequently hydrolyzed using the method described in Example 25(b). The crude mixture was purified by semi-preparative HPLC, to give 62 mg (31%) of the title compound. LC-MS (electrospray): m/z 574 (M+H).

Example 74

L-N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartic acid.

(a) A solution of 3,5-dichloro-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (50 mg), 3-ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI), (30 mg), 1-hydroxybenzotriazole hydrate (HBT), (28 mg) in dimethyl formamide (1 ml) was stirred at room temperature for 0.5 h followed by addition of a solution of *L*-di-*t*-butyl aspartate hydrochloride (52 mg) and triethylamine (32 mg) in dimethyl formamide (1 ml). After stirring for three days, the mixture was partitioned between water and ethyl acetate. The organic phase was washed with brine and then dried, filtered and concentrated. The residue was

chromatographed on silica gel eluted with ethyl acetate/light petroleum ether (1:4). Pure fractions were pooled and concentrated to give *L*-di-*t*-butyl N-[3,5-dichloro-4 (4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartate (68 mg, 83%).

(b) The above ester (48 mg) was hydrolyzed using the method described in Example 25(b) to give *L*-N-[3,5-dichloro-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartic acid (27 mg, 70%).

Example 75

D-di-*tert*-butyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamate

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (200 mg) was coupled with *D* - di*tert*buthyl glutamate hydrochloride (266 mg) using the method described in Example 25(a). The crude mixture was purified by semi-preparative HPLC, to give 170 mg (70%) of the title compound. LC-MS (electrospray): m/z 685 (M+H).

Example 76

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamic acid

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (200 mg) was coupled with *D*-di-*tert*-butyl glutamate hydrochloride (190 mg) using the method described in Example 25(a) and subsequently hydrolyzed using the method described in Example 25(b). The crude mixture was purified by semi-preparative HPLC, to give 60 mg (23%) of the title compound. LC-MS (electrospray): m/z 574 (M+H).

Example 77

L-O-*tert*-Butyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamine

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (200 mg) was coupled with *L*-O-*tert*-buthyl glutamine hydrochloride (230 mg) using the method described in Example 25(a). The crude mixture was purified by semi-preparative HPLC, to give 100 mg (44%) of the title compound. LC-MS (electrospray): m/z 629 (M+H).

Example 78

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamine

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (200 mg) was coupled with *L-tert*-butyl glutamine hydrochloride (230 mg) using the method described in Example 25(a) and subsequently hydrolyzed using the method described in Example 25(b). The crude mixture was purified by semi-preparative HPLC, to give 40 mg (15%) of the title compound. LC-MS (elctrospray): m/z 574 (M+H).

Example 79

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamine

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (200 mg) was coupled with *D*-glutamine hydrochloride (163 mg) using the method described in Example 25(a) and subsequently hydrolyzed using the method described in Example 25(b). The reaction mixture was concentrated *in vacuo*. The residue was subjected to semi-preparative HPLC, to give 30 mg (12%) of the title compound. LC-MS (electrospray): m/z 574 (M+H).

Example 80

L-O-Benzyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartic acid

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (200 mg) was coupled with *L*–O-Benzyl aspartic acid (266 mg) using the method described in Example 25(a). The crude mixture was purified by semi-preparative HPLC, to give 140 mg (38%) of the title compound. LC-MS (electrospray): m/z 650 (M+1).

Example 81

L-O-*tert*-Butyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]asparagine

3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (200 mg) was coupled with *L*-O-*tert*-butyl asparagine hydrochloride (170 mg) using the method described in Example 25(a). The crude mixture was purified by HPLC, to give 40 mg (16%) of the title compound. LC-MS (electrospray): m/z 558 (M+H).

Example 82

L-Methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]homoserine.

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)phenylacetic acid (134 mg) was coupled with *L*-homoserine (36 mg) using the method described in Example 25(a). The crude residue was dissolved in MeOH and heated at reflux with $SOCl_2$ for 2 h. After evaporaton of the solvent, the residue was chromatographed on column (silica gel, $CHCl_3$/MeOH 97:3). Pure fractions were pooled and concentrated to give 100 mg (64%) of the title compound.

Example 83

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]homoserine

L-Methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]-homoserine (100 mg) was hydrolyzed using the method described in Example 25(b). The crude product was purified by HPLC to give 30 mg (30%) of *L*-N-[3,5-dibromo-4-(4-hydroxy-3-isopropyl-phenoxy)phenylacetyl]homoserine

Example 84

D-Methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]homoserine.

3,5-Dibromo-4-(4-methoxy-3-isopropylphenoxy)phenylacetic acid (140 mg) was coupled with *L*-homoserine (36 mg) and re-esterified using the method described in Example 82. This gave 100 mg (64 %) of *D*-methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropyl-phenoxy)phenylacetyl]homoserine.

Example 85

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]homoserine

D-Methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]-homoserine (100 mg) was hydrolyzed using the method described in Example 25(b). The crude product was purified by HPLC to give 30 mg (30%) of *D*-N-[3,5-dibromo-4-(4-hydroxy-3- isopropyl-phenoxy)phenylacetyl]homoserine.

Example 86

N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]glycine

(a) A stirred mixture of 3,5-dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoic acid (9.56 g, 28.02 mmol), methyl glycine ester hydrochloride (5.28 g, 42.05 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (6.45 g, 33.64 mmol), 1-hydroxybenzotriazole (4.54 g, 33.60 mmol), CH_2Cl_2 (260 mL) and DMF (20 mL) was cooled with an ice-H_2O bath. N-methylmorpholine (5.7 g, 6.2 mL, 56.35 mmol) was added under N_2 and the reaction mixture was allowed to attain room temperature. After 18 h, CH_2Cl_2 was removed *in vacuo* and the residue partionated beetween EtOAc (300 mL) and H_2O (150 mL). The organic phase was successively washed with 1N HCl (2 x 150 mL), saturated aqueous $NaHCO_3$ (2 x 150 mL), and brine (2 x 150 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give 11.5 g of crude product as an orange solid. The crude product was purified by chromatography (Silica gel, 40 % EtOAc in hexane) to give 9.76 g (84 % yield) of slightly yellowish solid. ^1H NMR (500 MHz, $CDCl_3$): δ 7.82 (s, 2H), 6.78 (d, 1H, J = 2.7 Hz), 6.63 (d, 1H, J = 8.8 Hz), 6.61 (t, 1H, J = 4.9 Hz), 6.38 (dd,1H, J = 8.8, 3.3 Hz), 4.65 (s, 1H), 4.24 (d, 2H, J = 5 Hz), 3.82 (s, 3H), 3.16 (heptet, 1H, 6.6 Hz), 1.22 (d, 6H, J = 6.6 Hz); ^{13}C NMR: δ 170.18, 164.65, 150.66, 148.36, 136.26, 131.63, 130.57, 128.10, 115.76, 113.94, 112.28, 52.69, 41.87, 27.34, 22.38; MS-ESI$^-$ $[M-H]^-$= 410, 412, 414 (100:64:10).

(b) To a solution of methyl N-[3,5-dichloro-4-(4-hydroxy-3-isopropylphenoxy)-benzoyl] glycinate (7.30 g, 17.71 mmol) in THF (106 mL) was added 1 N aqueous lithium hydroxide solution (53 mL, 53 mmol). After 2h, the mixture was acidified with 1 N HCl and extracted with EtOAc (200 mL). The organic phase was washed with brine (2 x 75 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The concentrate was triturated with CH_2Cl_2(100 mL) and the white solid material obtained was dried in vacuo to give 6.85 g of the title product (97% yield). ^1H NMR (500 MHz, CD_3OD): δ 7.82 (s, 2H), 6.78 (d, 1H, J = 2.7 Hz), 6.63 (d, 1H, J = 8.8 Hz), 6.61 (t, 1H, J = 4.9 Hz), 6.38 (dd,1H, J = 8.8, 3.3 Hz), 4.65 (s, 1H), 4.24 (d, 2H, J = 5 Hz), 3.16 (heptet, 1H, 6.6 Hz), 1.22 (d, 6H, J = 6.6 Hz); ^{13}C NMR: δ 172.88, 167.20, 151.81, 151.34, 151.13, 137.67, 133.40, 131.39, 129.63, 116.41, 114.19, 113.28, 42.27, 28.19, 22.85; MS-ESI$^-$ $[M-H]^-$= 396, 398, 400 (100:64:10).

Example 87

N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]sarcosine

(a) To a solution of 3,5-dichloro-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (60 mg, 0.169 mmol) in CH_2Cl_2 (10 mL) cooled with an ice-H_2O bath was added sarcosine methyl ester hydrochloride (35.4 mg, 0.253 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (38.9 mg, 0.203 mmol) and 1-hydroxy-7-azabenzotriazole (27.6 mg, 0.203mmol) and N-methylmorpholine (34.2 mg, 37 *u*L, 0.338 mmol). The mixture was allowed to warm up to RT and left to stir overnight (ca. 18h). The mixture was taken up in EtOAc (50 mL) and H_2O (20 mL). The organic layer was separated and then it was washed successively with 1N HCl (2 x 25 mL), saturated $NaHCO_3$ aqueous solution (2 x 25 mL) and brine (2 x 25 mL). The organic extract was dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by chromatography (25 g silica gel, 30% EtOAc in hexane) to give 41 mg of purified material (55% yield). Satisfactory proton and LC-MS were obtained.

(b) To a solution of the product above (30 mg, 0.068 mmol) in anhydrous CH_2Cl_2 (3 mL) cooled with an ice-H_2O bath was added boron tribromide (0.7 mL, 1.0 M in CH_2Cl_2, 0.7 mmol). After 2h, the mixture was poured into ice-H_2O (25 mL). After 15 min of stirring, the product was extracted with EtOAc (50 mL). The organic extract was washed with brine (2 x 25 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product, a mixture of free acid and methyl ester , was dissolved in THF (2 mL) and 1N lithium hydroxide aqueous solution (1 mL) was added. After an hour, the mixture was acidified with 1N HCl and then extracted with EtOAc (25 mL). The EtOAc extract was washed with brine (2 x 15 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to give 35 mg of crude product. The crude product was purified by prep HPLC to give 12.3 mg of slightly yellowish solid as purified material (44% yield). Satisfactory proton and mass spectra were obtained.

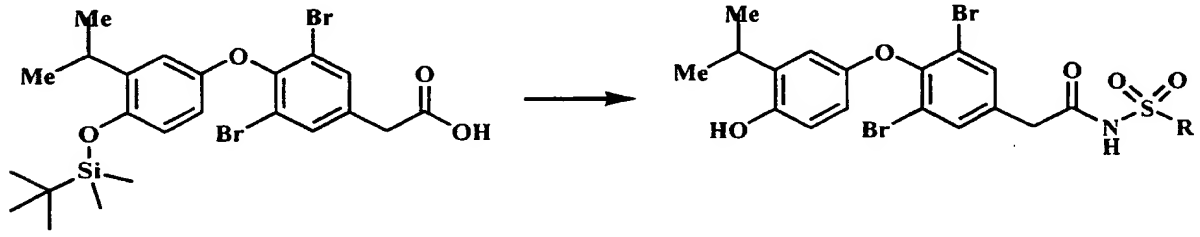
Example 88

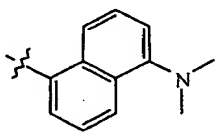
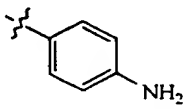
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl-5-dimethylamino-1-naphthalen esulphonamide

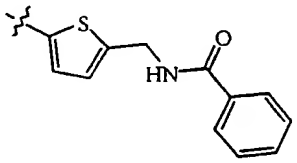
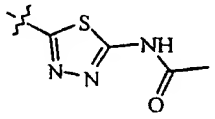
To a solution of the 3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetic acid (50 mg, 0.09 mmol), dimethylaminopyridine (4 mg, 0.018 mmol) and 5-dimethylamino-1-naphthalenesulphonamide (45 mg, 0.18 mmol) in 50% dichloromethane in dimethyl formamide (0.2 ml) was added a solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (28 mg, 0.13 mmol) and diisopropylethyl amine (17 mg, 0.13 mmol) in 50% methylene chloride in dimethyl formamide (0.2 ml). The reaction mixture was vortexed and allowed to stand at room temperature for 6 hours. A solution of ammonium fluoride (0.5 M in methanol; 0.4 ml) was added. After 16 hours, the reaction mixture was evaporated to dryness, re-dissolved in a solvent mixture containing 90% methanol, 10% water and 0.1% trifluoroacetic acid (2 ml) and purified by preparative HPLC (YMC S5 ODS 30 x 250 mm: 50-100% solvent B in 30 min: solvent A - 90% water, 10% methanol, 0.1% trifluoroacetic acid; solvent B – 10% water, 90% methanol, 0.1% trifluoroacetic acid: flow rate 25 ml per min: detection 220 nm). The yield was 10.1 mg (16%).

Example 89-91

These compounds were prepared and purified in a similar manner as above. For a table of Examples 88-91 comprising the coupled sulphonamide, retention times and mass spectra, see Scheme below.

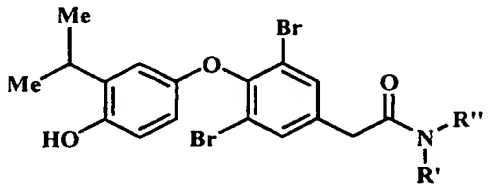


Example	R	MS (ESI+)	R_t (min)[1]
88		677	6.9
89		598	4.3

90		722	5.1
91		648	4.9

[1]YMC ODS 4.6 x 50 mm: 50-100% solvent B in 8 min: solvent A - 90% water, 10% methanol, 0.2% phosphoric acid; solvent B – 10% water, 90% methanol, 0.2% phosphoric acid: flow rate 2.5 ml per min: detection 220 nm

Examples 92-191



Procedures for the synthesis of the library compounds indicated in the Table below are described in Lawrence, R.M.; Biller, S.A.; Fryszman, O.M.; Poss, M.A. *Synthesis* **1997**, 553.

[1]HPLC retention time in minutes and gradient method. Reverse phase HPLC analyses performed on YMC S5 ODS 4.6 x 50 mm analytical columns, detection at 220 nm, and 4 minute gradient elutions by either: method a, 0% B, 100% A to 100% B, 0% A; or method b, 20% B, 80% A to 100% B, 0% A, where solvent A is 90% water, 10% methanol, 0.2% phosphoric acid and solvent B is 10% water, 90% methanol, 0.2% phosphoric acid.
[2]MS result obtained on a Micromass Platform II using electrospray, both positive and negative ion modes.
[3]Method A examples were prepared by synthesis procedure A in the reference cited above. In these examples, a second basic nitrogen is present in the amine coupling partner. However, only one nitrogen is capable of giving the normal acylation product. Method B examples were prepared by procedure C in the reference cited above.

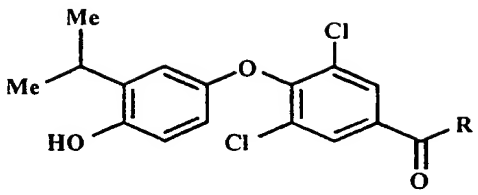
Example	-NR'R"	HPLC[1]	MS[2]	Formula	Method[3]
92	3-(AMINOMETHYL)PYRIDINE	2.76,a	m/z 534.84 (M+H)	C23H22Br2N2O3	A
93	2-(2-AMINOETHYL)PYRIDINE	2.73,a	m/z 548.83 (M+H)	C24H24Br2N2O3	A
94	3-(2-AMINOETHYL)PYRIDINE	2.73,a	m/z 548.82 (M+H)	C24H24Br2N2O3	A
95	2-(AMINOMETHYL)PYRIDINE	2.84,a	m/z 534.85 (M+H)	C24H30Br2N2O3	A
96	4-(AMINOMETHYL)PYRIDINE	2.74,a	m/z 534.82 (M+H)	C24H30Br2N2O3	A
97	1-(4-METHOXYPHENYL)PIPERAZINE DIHYDROCHLORIDE	3.33,a	m/z 618.81 (M+H)	C29H32Br2N2O3	A

Example	-NR'R''	HPLC[1]	MS[2]	Formula	Method[3]
98	1-(2-FLUOROPHENYL)PIPERAZINE	3.53,a	m/z 607.16 (M+H)	C34H32Br2N2O3	A
99	2-(2-(AMINOMETHYL)PHENYLTHIO)BENZYL ALCOHOL	4.42,a	m/z 671.97 (M+H)	C31H29Br2NO4S	B
100	2-(1-CYCLOHEXENYL)ETHYLAMINE	4.56,a	m/z 551.98 (M+H)	C25H29Br2NO3	B
101	2-AMINOINDAN	4.44,a	m/z 559.88 (M+H)	C26H25Br2NO3	B
102	2-AMINOMETHYLBENZODIOXAN	4.39,a	m/z 591.93 (M+H)	C26H25Br2NO5	B
103	3-PHENYL-1-PROPYLAMINE	4.44,a	m/z 560.00 (M-H)	C26H27Br2NO3	B
104	2-(P-TOLYL)ETHYLAMINE	4.48,a	m/z 559.95 (M-H)	C26H27Br2NO3	B
105	1-(3-AMINOPROPYL)-2-PYRROLIDINONE	3.97,a	m/z 568.97 (M+H)	C24H28Br2N2O4	B
106	BETA-ALANINE 4-METHOXY-BETA-NAPHTHYLAMIDE	4.52,a	m/z 670.88 (M+H)	C31H30Br2N2O5	B
107	2-CHLOROBENZYLAMINE	4.38,a	m/z 612.98 (M+?)	C24H22Br2ClNO3	B
108	2-AMINOMETHYL-3-CHLORODIPHENYLETHER	4.65,a	m/z 660.08 (M+H)	C30H26Br2ClNO4	B
109	DL-ALPHA-AMINO-EPSILON-CAPROLACTAM	4.03,a	m/z 554.86 (M+H)	C23H26Br2N2O4	B
110	L-PHENYLALANINOL	4.22,a	m/z 577.92 (M+H)	C26H27Br2NO4	B
111	4-(1,2,3-THIADIAZOL-4-YL)BENZYLAMINE	4.21,a	m/z 617.69 (M+H)	C26H23Br2N3O3S	B
112	2-AMINOMETHYLTHIOPHENE	4.21,a	m/z 539.84 (M+H)	C22H21Br2NO3S	B
113	1-(1-NAPHTHYL)ETHYLAMINE	4.54,a	m/z 597.83 (M+H)	C29H27Br2NO3	B
114	3-CHLORO-4-METHYL BENZYLAMINE	4.53,a	m/z 581.80 (M+H)	C25H24Br2ClNO3	B
115	TETRAHYDROFURFURYLAMINE	4.07,a	m/z 527.90 (M+H)	C22H25Br2NO4	B
116	2,4-DICHLOROPHENETHYLAMINE	4.66,a	m/z 615.73 (M+H)	C25H23Br2Cl2NO3	B
117	ETHYL 4-AMINO-1-PIPERIDINECARBOXYLATE	4.21,a	m/z 599.05 (M+H)	C25H30Br2N2O5	B
118	2,6-DIFLUOROBENZYLAMINE	4.25,a	m/z 569.82 (M+H)	C24H21Br2F2NO3	B
119	2-IODOBENZYLAMINE	4.46,a	m/z 659.45 (M+H)	C24H22Br2INO3	B
120	2-METHYLBENZYLAMINE	4.38,a	m/z 547.89 (M+H)	C25H25Br2NO3	B
121	BENZYLAMINE	4.27,a	m/z 533.85 (M+H)	C24H23Br2NO3	B
122	3-METHYLBENZYLAMINE	4.38,a	m/z 547.89 (M+H)	C25H25Br2NO3	B
123	2-METHOXYPHENETHYLAMINE	4.41,a	m/z 577.81 (M+H)	C26H27Br2NO4	B
124	3-METHOXYPHENETHYLAMINE	4.35,a	m/z 577.87 (M+H)	C26H27Br2NO4	B
125	2-ETHOXYBENZYLAMINE	4.42,a	m/z 577.86 (M+H)	C26H27Br2NO4	B
126	(R)-(-)-1-CYCLO-HEXYLETHYLAMINE	4.56,a	m/z 553.90 (M+H)	C25H31Br2NO3	B
127	4-METHOXYPHENETHYLAMINE	4.32,a	m/z 577.83 (M+H)	C26H27Br2NO4	B
128	2-FLUOROBENZYLAMINE	4.27,a	m/z 551.85 (M+H)	C24H22Br2FNO3	B
129	2-CHLORO-6-METHYLBENZYLAMINE	4.48,a	m/z 581.85 (M+H)	C25H24Br2ClNO3	B

Example	-NR'R"	HPLC[1]	MS[2]	Formula	Method[3]
130	4-CHLOROBENZYLAMINE	4.42,a	m/z 567.83 (M+H)	C24H22Br2ClNO3	B
131	BETA-METHYLPHENETHYLAMINE	4.43,a	m/z 561.88 (M+H)	C26H27Br2NO3	B
132	1,1-DI(P-ANISYL)METHYLAMINE	4.47,a	m/z 669.88 (M+H)	C32H31Br2NO5	B
133	MAYBRIDGE BTB 12133	4.18,a	m/z 623.84 (M+H)	C27H29Br2NO6	B
134	DL-2-AMINO-1-PENTANOL	4.12,a	m/z 529.91 (M+H)	C22H27Br2NO4	B
135	L-PHENYLALANINE P-NITROANILIDE	4.56,a	m/z 711.88 (M+H)	C32H29Br2N3O6	B
136	ETHYL 3-AMINOBUTYRATE	4.16,a	m/z 557.85 (M+H)	C23H27Br2NO5	B
137	(1S,2R)-(+)-2-AMINO-1,2-DIPHENYLETHANOL	4.28,a	m/z 639.92 (M+H)	C31H29Br2NO4	B
138	2-FLUOROPHENETHYLAMINE	4.37,a	m/z 565.90 (M+H)	C25H24Br2FNO3	B
139	2-ETHYLHEXYLAMINE	4.70,a	m/z 555.93 (M+H)	C25H33Br2NO3	B
140	3-FLUOROPHENETHYLAMINE	4.36,a	m/z 565.85 (M+H)	C25H24Br2FNO3	B
141	(1S,2S)-(+)-2-AMINO-3-METHOXY-1-PHENYL-1-PROPANOL	4.19,a	m/z 607.89 (M+H)	C27H29Br2NO5	B
142	NONYLAMINE	4.88,a	m/z 569.95 (M+H)	C26H35Br2NO3	B
143	2,5-DICHLOROBENZYLAMINE	4.49,a	m/z 601.72 (M+H)	C24H21Br2Cl2NO3	B
144	2-METHYLCYCLOHEXYLAMINE	4.44,a	m/z 539.91 (M+H)	C24H29Br2NO3	B
145	3-METHYLCYCLOHEXYLAMINE	4.51,a	m/z 539.90 (M+H)	C24H29Br2NO3	B
146	3-N-PROPOXYPROPYLAMINE	4.30,a	m/z 543.90 (M+H)	C23H29Br2NO4	B
147	2,3-DIMETHYLBENZYLAMINE	4.48,a	m/z 561.91 (M+H)	C26H27Br2NO3	B
148	3-CHLOROBENZYLAMINE	4.40,a	m/z 567.79 (M+H)	C24H22Br2ClNO3	B
149	4-TERT-BUTYLCYCLOHEXYLAMINE	4.80,a	m/z 581.97 (M+H)	C27H35Br2NO3	B
150	(1S,2S)-(+)-THIOMICAMINE	3.94,a	m/z 639.80 (M+H)	C27H29Br2NO5S	B
151	2,4-DIMETHYLBENZYLAMINE	4.49,a	m/z 561.89 (M+H)	C26H27Br2NO3	B
152	2-AMINOETHYL PHENYL SULFIDE	4.44,a	m/z 579.83 (M+H)	C25H25Br2NO3S	B
153	PHENETHYLAMINE	4.36,a	m/z 547.87 (M+H)	C25H25Br2NO3	B
154	TYRAMINE	4.04,a	m/z 563.86 (M+H)	C25H25Br2NO4	B
155	L-TYROSINE METHYL ESTER	4.01,a	m/z 621.97 (M+H)	C27H27Br2NO6	B
156	BENZHYDRYLAMINE	4.52,a	m/z 609.82 (M+H)	C30H27Br2NO3	B
157	4-METHOXYBENZYLAMINE	4.25,a	m/z 563.85 (M+H)	C25H25Br2NO4	B
158	2,3-DICHLOROBENZYLAMINE	4.52,a	m/z 601.71 (M+H)	C24H21Br2Cl2NO3	B
159	GLYCINE N-BUTYL ESTER HYDROCHLORIDE	4.03,b	m/z 557.85 (M+H)	C23H27Br2NO5	B
160	D-(-)-ALPHA-PHENYLGLYCINE ETHYL ESTER HYDROCHLORIDE	4.11,b	m/z 605.84 (M+H)	C27H27Br2NO5	B
161	4-CHLORO-2-FLUOROBENZYLAMINE HYDROCHLORIDE	4.27,b	m/z 585.80 (M+H)	C24H21Br2ClFNO3	B
162	TRANS-2-PHENYLCYCLOPROPYLAMINE HYDROCHLORIDE	4.22,b	m/z 559.86 (M+H)	C26H25Br2NO3	B

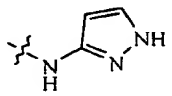
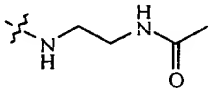
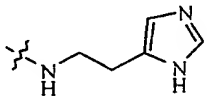
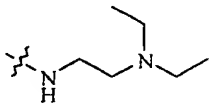
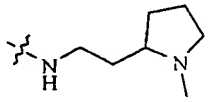
Example	-NR'R''	HPLC[1]	MS[2]	Formula	Method[3]
163	ETHYL 4-AMINOBUTYRATE HYDROCHLORIDE	3.87,b	m/z 557.85 (M+H)	C23H27Br2NO5	B
164	DL-HOMOCYSTEINE THIOLACTONE HYDROCHLORIDE	3.65,b	m/z 543.80 (M+H)	C21H21Br2NO4S	B
165	4-NITROBENZYLAMINE HYDROCHLORIDE	3.99,b	m/z 578.85 (M+H)	C24H22Br2N2O5	B
166	NORPHENYLEPHRINE HYDROCHLORIDE	3.60,b	m/z 579.84 (M+H)	C25H25Br2NO5	B
167	GLYCINE ETHYL ESTER HYDROCHLORIDE	3.71,b	m/z 529.87 (M+H)	C21H23Br2NO5	B
168	DL-ALANINE ETHYL ESTER HYDROCHLORIDE	3.83,b	m/z 543.86 (M+H)	C22H25Br2NO5	B
169	SARCOSINE ETHYL ESTER HYDROCHLORIDE	3.79,b	m/z 543.92 (M+H)	C22H25Br2NO5	B
170	4-NITRO-N-PROPYLBENZYL AMINE HYDROCHLORIDE	4.29,b	m/z 620.89 (M+H)	C27H28Br2N2O5	B
171	PIPERIDINE	3.98,b	m/z 511.93 (M+H)	C22H25Br2NO3	B
172	3-METHYLPIPERIDINE	4.14,b	m/z 525.91 (M+H)	C23H27Br2NO3	B
173	3-(HYDROXYMETHYL)-PIPERIDINE	3.66,b	m/z 541.89 (M+H)	C23H27Br2NO4	B
174	1,2,3,4-TETRAHYDROISOQUINOLINE	4.23,b	m/z 559.85 (M+H)	C26H25Br2NO3	B
175	2-ETHYLPIPERIDINE	4.25,b	m/z 539.90 (M+H)	C24H29Br2NO3	B
176	3,4-DICHLORO-N-ETHYLBENZYLAMINE	4.54,b	m/z 629.75 (M+H)	C26H25Br2Cl2NO3	B
177	2-METHYLPYRROLIDINE	3.99,b	m/z 511.90 (M+H)	C22H25Br2NO3	B
178	N-ETHYL-N-PROPYLAMINE	4.11,b	m/z 513.89 (M+H)	C22H27Br2NO3	B
179	4-METHYLPIPERIDINE	4.15,b	m/z 525.91 (M+H)	C23H27Br2NO3	B
180	(S)-(+)-2-(METHOXYMETHYL)PYRROLIDINE	3.99,b	m/z 541.90 (M+H)	C23H27Br2NO4	B
181	N-BENZYLETHANOLAMINE	4.01,b	m/z 577.86 (M+H)	C26H27Br2NO4	B
182	DIBENZYLAMINE	4.56,b	m/z 623.79 (M+H)	C31H29Br2NO3	B
183	4-BENZYL-4-HYDROXYPIPERIDINE	4.12,b	m/z 617.88 (M+H)	C29H31Br2NO4	B
184	(R)(-)-2-BENZYLAMINO-1-BUTANOL	4.16,b	m/z 605.83 (M+H)	C28H31Br2NO4	B
185	N-(N-ETHYLAMINOACETYL)-2,6-DIMETHYLANILINE	4.00,b	m/z 632.69 (M+H)	C29H32Br2N2O4	B
186	N-ETHYL-O-METHOXYBENZYLAMINE	4.35,b	m/z 591.93 (M+H)	C27H29Br2NO4	B
187	MAYBRIDGE NRB 01961	4.40,b	m/z 647.88 (M+H)	C30H33Br2NO5	B
188	2-((N-ETHYLAMINO)METHYL)-4-NITROPHENOL	4.05,b	m/z 622.80 (M+H)	C26H26Br2N2O6	B
189	MAYBRIDGE SEW 01484	4.48,b	m/z 671.89 (M+H)	C31H29Br2NO4S	B
190	3-AZABICYCLO-[3.2.2]NONANE	4.28,b	m/z 551.89 (M+H)	C25H29Br2NO3	B
191	N-(2-METHOXY-ETHYL)ETHYLAMINE	3.89,b	m/z 529.88 (M+H)	C22H27Br2NO4	B

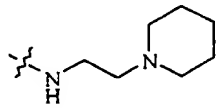
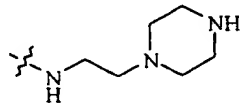
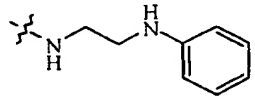
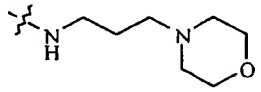
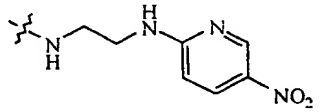
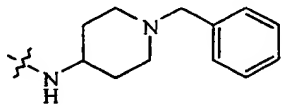
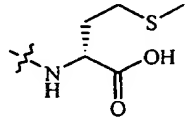
Examples 192-203



General Procedure

3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoic acid was coupled with the appropriate amino acid. using the general procedure outlined for Examples 3-24. The residue was subjected to semi-preparative HPLC, using the same gradient elution as outlined for Examples 3-24. The amine part "R" and the stereochemistry of the aminoacids is indicated in the table below. Retention times, yields and the mass of the individual products are also given below.

Example	R	Yield (%)	MS m/z (M+H)$^+$	HPLC
192		64	407.3	7.3
193		61	426.1	7.1
194		59	435.2	6.6
195		40	440.1	6.7
196		88	452.3	6.6

197		76	452.2	6.7
198		71	453.2	6.5
199		39	460.1	7.6
200		55	467.9	6.7
201		31	506.3	7.5
202		72	514.4	7.0
203		52	473.2	8.0

Example 204

2-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-thiazole acetic acid

(a) A reaction mixture of 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)phenyl acetamide (150 mg) and Lawesson's reagent (100 mg) in dioxane (3 mL) was stirred at room temperature for 15 hours. The resulting suspension as filtered and poured onto ice-water and stirred. The water phase was extracted with EtOAc (3x7 mL) and the combined organic phases were washed with water. The organic phase was dried over Na_2SO_4. concentrated and gave 153 mg of crude 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)phenyl thioamide. The crude product was used directly in the next step.

(b) To a suspension of 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)phenyl thioamide (80 mg) in EtOH (2 mL), ethylchloroacetoacetonate (0.03 mL) was added. The

mixture was stirred in a closed tube at 75 C for 2 h. The reaction mixture was concentrated and EtOAc and water was added. The water phase was extracted with EtOAc (3x5 mL) and the combined organic phases were washed with $NaHCO_3$ (sat. solution). The organic phase was dried over Na_2SO_4, concentrated and purified by chromatography (silica gel, 15 % EtOAc/p-ether). This gave 80 mg (86%) of ethyl-2-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-thiazole acetate.

(c) $BF_3.Et_2$ (0.06 mL) was added slowly to a solution of the ethyl ester (60 mg) in CH_2Cl_2 (4 mL). The reaction mixture was stirred at room temperature for 2 days. Water was added. The water phase was extracted with EtOAc (3x5 mL) and the combined organic phases were washed with an aqueous solution of HCl (1N). The organic phase was dried over Na_2SO_4, concentrated and purified by semi-preparative HPLC. This gave 20 mg (37 %) of the title compound.

Example 205

2-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-methylthiazole

(a) 3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)phenyl thioamide (70 mg) in EtOH (2 mL) was reacted with ethylchloroacetoacetonate (0.014 mL) using the method described in Example 204(b). The crude product was purified by chromatography (silica gel, 15 % EtOAc/p-ether). This gave 60 mg (78 %) of 2-[3,5-dibromo-4-(4-methoxy-3-isopropylphenoxy)benzyl]-4-methylthiazole.

(b) The above methoxy compound (50 mg) was demethylated with $BF_3.Et_2$ (0.06 mL), using the method described above. The crude mixture was purified by semi-preparative HPLC. This gave 20 mg (41 %) of the title compound.

Example 206

3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)phenylformylimino diacetic acid

(a) To a solution of 3,5-dichloro-4-(4-methoxy-3-isopropylphenoxy)benzoic acid (60 mg, 0.169 mmol) in CH_2Cl_2 (10 mL) cooled with an ice-H_2O bath was added diethyliminodiacetate (35.4 mg, 0.253 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (38.9 mg, 0.203 mmol) and 1-hydroxy-7-azabenzotriazole (27.6 mg, 0.203mmol) . The mixture was allowed to warm up to room temperature and left to

stir overnight (ca. 18h). The mixture was taken up in EtOAc (50 mL) and H_2O (20 mL). The organic layer was separated and then it was washed successively with 1N HCl (2 x 25 mL), saturated $NaHCO_3$ aqueous solution (2 x 25 mL) and brine (2 x 25 mL). The organic extract was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by chromatography (25 g silica gel,15% EtOAc in hexane) to give 31 mg of purified material (35% yield). Satisfactory proton and LC-MS were obtained.

(b) To a solution of above ethyl ester (25 mg, 0.047 mmol) in anhydrous CH_2Cl_2 (3 mL) cooled with an ice-H_2O bath was added boron tribromide (0.7 mL, 1.0 M in CH_2Cl_2, 0.7 mmol). After 2h, the mixture was poured into ice-H_2O (25 mL). After 15 min of stirring, the product was extracted with EtOAc (50 mL). The organic extract was washed with brine (2 x 25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product, a mixture of free acid and methyl ester , was dissolved in THF (2 mL) and 1N lithium hydroxide aqueous solution (1 mL) was added. After an hour, the mixture was acidified with 1N HCl and then extracted with EtOAc (25 mL). The EtOAc extract was washed with brine (2 x 15 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to give 27.7 mg of crude product. The crude product was purified by prep HPLC to give 9.2 mg (38 %) of of the title compound as a slightly yellow solid. Satisfactory proton and mass spectra were obtained.

Example 207

N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]-beta-alanine

(a) 3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoic acid (50 mg, 0.116 mmol), beta-alanine methyl ester hydrochloride (70 mg, 0.42 mmol), and hydroxy-benzotriazole (78 mg, 0.57 mmol) were dissolved in dichloromethane (0.6 mL), N,N-dimethylformamide (0.2 mL) and triethyl amine (0.12 mL, 0.58 mmol). The solution was cooled to 0 °C and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrogen chloride (110 mg, 0.58 mmol) was added. The reaction was warmed to room temperature and stirred for 12 hours. The reaction was diluted with dichloromethane (100 mL) and washed with water (2 x 150 mL). The organic layer was washed once with brine (100 ml), dried over sodium sulfate and concentrated *in vacuo*. The methyl ester (50 mg, 90 % yield) was purified by chromathography (silica gel, 7:3 hexane/ethyl acetate).

(b) The crude ester was dissolved in 1.0 mL of methanol and 0.4 mL of 1 N sodium hydroxide. The hydrolysis was complete in 2 hours. The methanol was removed and the

aqueous layer was acidified with aqueous hydrochloric acid (1 N). The aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (2 x 75 mL) and dried over sodium sulfate. The organic layer was concentrated *in vacuo*. The title compound (51 mg, 98%) was obtained without further purification. Satisfactory ^{1}H-NMR, ^{13}C-NMR and mass spectra was obtained for the title compound.

Example 208

N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]-beta-alanine

(a) The ester was prepared by adding the reagents to the reaction in the manner described in Example 207. The starting acid (122 mg, 0.356 mmol), B-alanine methyl ester hydrochloride, and hydroxybenzotriazole (240 mg, 1.76 mmol) were dissolved in triethyl amine (0.6 mL, 2.5 mmol), dichloromethane 1.2 mL, and 0.8 mL of dimethylamide. The1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrogen chloride (110 mg, 0.58 mmol) was added in the manner as described above. The ester (75 mg, 50 %) was isolated without further purification.

(b) The ester was dissolved in 3.0 mL of methanol and 1.6 mL of 1 N sodium hydroxide using the procedure described for title acid. The title acid (72 mg, 98 % yield) was obtained from the reaction. The acid was further purified by preparative HPLC using a YMC ODS 20 x 100 mm column which yielded 53.6 mg (74 % yield) of the purified acid.

Example 209

L-N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]serine

3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoic acid (122 mg) was coupled with L-serin methyl ester hydrochloride using the method described in Example 207(a) and subsequently hydrolyzed using the method described in Example 207(b). The crude mixture was purified as above. Satisfactory ^{1}H-NMR, ^{13}C-NMR and mass spectra was obtained for the title compound.

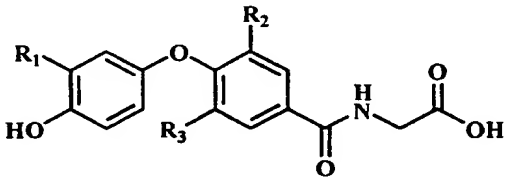
Example 210

D-N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]serine

3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoic acid (122 mg) was coupled with D-serin methyl ester hydrochloride using the method described in Example 207(a) and subsequently hydrolyzed using the method described in Example 207(b). The crude mixture was purified as above. Satisfactory ^{1}H-NMR, ^{13}C-NMR and mass spectra was obtained for the title compound.

Examples 211-228

The compounds indicated in the table below are all examples of further compounds, that can readily be prepared via the synthetic procedure described in Example 86.



Example	R_1	R_2	R_3
211	Isopropyl	Me	Me
212	Isopropyl	Me	Br
213	Isopropyl	Me	Cl
214	Isopropyl	Me	I
215	Isopropyl	I	I
216	Isopropyl	I	Cl
217	Isopropyl	I	Br
218	Isopropyl	Br	Cl
219	I	Me	Me
220	I	Me	Br
221	I	Me	Cl
222	I	Me	I
223	I	I	I
224	I	Br	Cl
225	I	Br	Br
226	I	Cl	Cl
227	I	I	Br
228	I	I	Cl

Examples 229-231

N-[3,5-Dichloro-4-(4-hydroxy-3-bromophenoxy)benzoyl]glycine

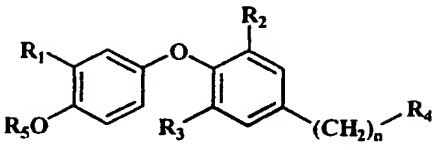
N-[3,5-Dichloro-4-(4-hydroxy-3-methylphenoxy)benzoyl]glycine

N-[3,5-Dichloro-4-(4-hydroxy-3-ethylphenoxy)benzoyl]glycine

These compounds were all prepared by a method analogous to that used in Example 86. Satisfactory ^{1}H-NMR, ^{13}C-NMR and mass spectra were obtained for all three compounds.

What is claimed is:

1. A compound having the formula



wherein

n is an integer from 0 to 4;

R_1 is halogen, trifluoromethyl, or alkyl of 1 to 6 carbons or cycloalkyl of 3 to 7 carbons;

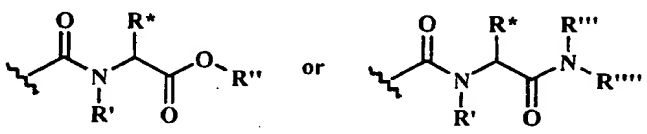
R_2 and R_3 are the same or different and are hydrogen, halogen, alkyl of 1 to 4 carbons, at least one of R_2 and R_3 being other than hydrogen;

R_4 is a heteroaromatic moiety which may be substituted or unsubstituted and is linked to $(CH_2)_n$ via a nitrogen atom or a carbon atom; an amine (NR'R"), including those in which the amine is derived from an alpha amino acid of either natural (L) or unnatural (D) stereochemistry; an acylsulphonamide ($CONHSO_2R'$); or a carboxylic acid amide (CONR'R'') with the proviso that when n equals zero (n = 0), then R_4 can only be a carboxylic acid amide or an acylsulphonamide;

R_5 is hydrogen or an acyl (such as acetyl or benzoyl) or other group capable of bioconversion to generate the free phenol structure (wherein R_5 = H);

including all stereoisomers thereof, prodrug esters thereof, and pharmaceutically acceptable salts thereof.

2. A compound as defined in Claim 1 where R_4 is a carboxylic acid amide (CONR'R'') in which the amine portion of the carboxylic amide can be derived from an achiral or a L or D alpha amino acid such as when the general structure -CONR'R'' can be represented by



and R', R'', R''' and R'''' are the same or different and are independently selected from hydrogen, alkyl, aryl and heteroaryl, substituted or unsubstituted, and R* may be hydrogen, alkyl, aryl and heteroaryl, substituted or unsubstituted, and may also be any of the side chains found in the naturally occuring alpha-amino acids

3. The compound as defined in Claim 2 where R' and R* are connected to form a 4 to 8-membered ring.

4. The compound as defined in Claim 2 where R' and R* comprise consecutive -(CH_2)- groups to form proline or homoproline.

5. The compound as defined in Claim 1 where n is 0 or 1 or 2.

6. The compound as defined in Claim 1 wherein R_2 and R_3 are each independently halogen.

7. The compound as defined in Claim 1 wherein R_2 and R_3 are each independently an alkyl group.

8. The compound as defined in Claim 1 wherein one of R_2 and R_3 is halogen and the other is an alkyl group.

9. The compound as defined in Claim 1 wherein one of R_2 and R_3 is halogen and the other is hydrogen.

10. The compound as defined in Claim 1 wherein one of R_2 and R_3 is alkyl and the other is hydrogen.

11. The compound as defined in Claim 1 wherein R_2 and R_3 are independently Cl, Br, methyl or ethyl.

12. The compound as defined in Claim 1 wherein R_1 is isopropyl.

13. The compound as defined in Claim 1 wherein R_4 is heteroaromatic hydrocarbon, carboxylic acid amide, or an acylsulphonamide.

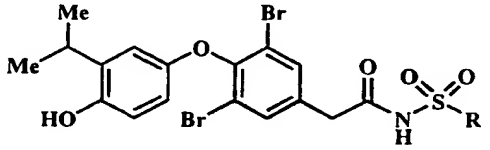
14. The compound as defined in Claim 1 wherein R_5 is hydrogen.

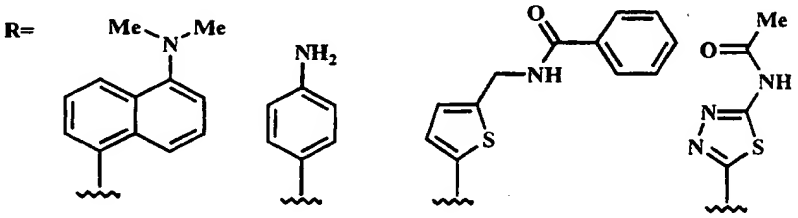
15. The compound as defined in Claim 1 which is
3,5-Dimethyl-4-(4-hydroxy-3-isopropylphenoxy)benzyltetrazole,
3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzyltetrazole,
2-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-thiazole acetic acid,

2-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzyl]-4-methylthiazole,

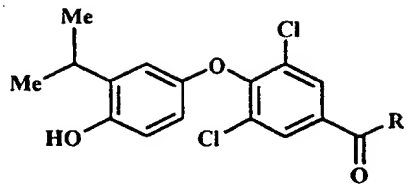
16. The compound as defined in Claim 1 which is
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-5-hydroxy-1-naphthalenesulphonamide,
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-toluenesulphonamide,
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-nitrobenzenesulphonamide,
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl sulfamide,
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-5-dimethylamino-1-naphthalenesulphonamide,
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-aminobenzenesulphonamide,
Methyl-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-2-sulphonamide] benzoate,
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-2-aminobenzenesulphonamide,
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-2-toluenesulphonamide,
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-(2-aminoethyl)benzenesulphonamide,
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-(2-aminomethyl)benzenesulphonamide,
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-3-nitrobenzenesulphonamide,
3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl-4-chlorobenzenesulphonamide,

and the compounds shown below,

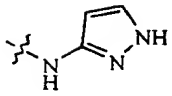
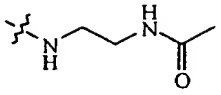
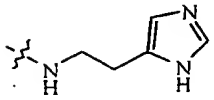
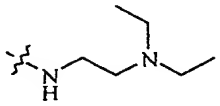
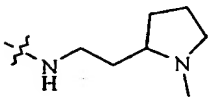
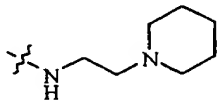
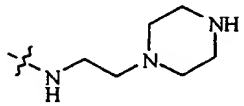
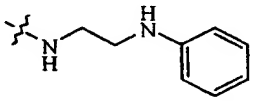
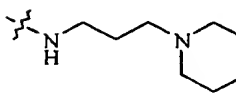
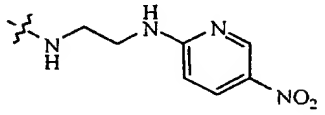
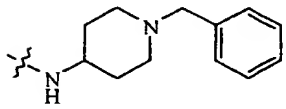




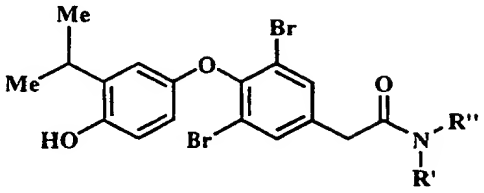
17. The compound as defined in Claim 1 which is in the table below,



R=

and the compounds indicated in the table below,



-NR'R"	Formula
3-(AMINOMETHYL)PYRIDINE	C23H22Br2N2O3
2-(2-AMINOETHYL)PYRIDINE	C24H24Br2N2O3

-NR'R"	Formula
3-(2-AMINOETHYL)PYRIDINE	C24H24Br2N2O3
2-(AMINOMETHYL)PYRIDINE	C24H30Br2N2O3
4-(AMINOMETHYL)PYRIDINE	C24H30Br2N2O3
1-(4-METHOXYPHENYL)PIPERAZINE DIHYDROCHLORIDE	C29H32Br2N2O3
1-(2-FLUOROPHENYL)PIPERAZINE	C34H32Br2N2O3
2-(2-(AMINOMETHYL)PHENYLTHIO)BENZYL ALCOHOL	C31H29Br2NO4S
2-(1-CYCLOHEXENYL)ETHYLAMINE	C25H29Br2NO3
2-AMINOINDAN	C26H25Br2NO3
2-AMINOMETHYLBENZODIOXAN	C26H25Br2NO5
3-PHENYL-1-PROPYLAMINE	C26H27Br2NO3
2-(P-TOLYL)ETHYLAMINE	C26H27Br2NO3
1-(3-AMINOPROPYL)-2-PYRROLIDINONE	C24H28Br2N2O4
BETA-ALANINE 4-METHOXY-BETA-NAPHTHYLAMIDE	C31H30Br2N2O5
2-CHLOROBENZYLAMINE	C24H22Br2ClNO3
2-AMINOMETHYL-3-CHLORODIPHENYLETHER	C30H26Br2ClNO4
DL-ALPHA-AMINO-EPSILON-CAPROLACTAM	C23H26Br2N2O4
L-PHENYLALANINOL	C26H27Br2NO4
4-(1,2,3-THIADIAZOL-4-YL)BENZYLAMINE	C26H23Br2N3O3S
2-AMINOMETHYLTHIOPHENE	C22H21Br2NO3S
1-(1-NAPHTHYL)ETHYLAMINE	C29H27Br2NO3
3-CHLORO-4-METHYL BENZYLAMINE	C25H24Br2ClNO3
TETRAHYDROFURFURYLAMINE	C22H25Br2NO4
2,4-DICHLOROPHENETHYLAMINE	C25H23Br2Cl2NO3
ETHYL 4-AMINO-1-PIPERIDINECARBOXYLATE	C25H30Br2N2O5
2,6-DIFLUOROBENZYLAMINE	C24H21Br2F2NO3
2-IODOBENZYLAMINE	C24H22Br2INO3
2-METHYLBENZYLAMINE	C25H25Br2NO3
BENZYLAMINE	C24H23Br2NO3
3-METHYLBENZYLAMINE	C25H25Br2NO3
2-METHOXYPHENETHYLAMINE	C26H27Br2NO4
3-METHOXYPHENETHYLAMINE	C26H27Br2NO4
2-ETHOXYBENZYLAMINE	C26H27Br2NO4
(R)-(-)-1-CYCLO-HEXYLETHYLAMINE	C25H31Br2NO3
4-METHOXYPHENETHYLAMINE	C26H27Br2NO4
2-FLUOROBENZYLAMINE	C24H22Br2FNO3
2-CHLORO-6-METHYLBENZYLAMINE	C25H24Br2ClNO3
4-CHLOROBENZYLAMINE	C24H22Br2ClNO3
BETA-METHYLPHENETHYLAMINE	C26H27Br2NO3
1,1-DI(P-ANISYL)METHYLAMINE	C32H31Br2NO5
MAYBRIDGE BTB 12133	C27H29Br2NO6
DL-2-AMINO-1-PENTANOL	C22H27Br2NO4
L-PHENYLALANINE P-NITROANILIDE	C32H29Br2N3O6
ETHYL 3-AMINOBUTYRATE	C23H27Br2NO5
(1S,2R)-(+)-2-AMINO-1,2-DIPHENYLETHANOL	C31H29Br2NO4
2-FLUOROPHENETHYLAMINE	C25H24Br2FNO3
2-ETHYLHEXYLAMINE	C25H33Br2NO3
3-FLUOROPHENETHYLAMINE	C25H24Br2FNO3
(1S,2S)-(+)-2-AMINO-3-METHOXY-1-PHENYL-1-PROPANOL	C27H29Br2NO5
NONYLAMINE	C26H35Br2NO3
2,5-DICHLOROBENZYLAMINE	C24H21Br2Cl2NO3
2-METHYLCYCLOHEXYLAMINE	C24H29Br2NO3
3-METHYLCYCLOHEXYLAMINE	C24H29Br2NO3
3-N-PROPOXYPROPYLAMINE	C23H29Br2NO4
2,3-DIMETHYLBENZYLAMINE	C26H27Br2NO3
3-CHLOROBENZYLAMINE	C24H22Br2ClNO3
4-TERT-BUTYLCYCLOHEXYLAMINE	C27H35Br2NO3

-NR'R"	Formula
(1S,2S)-(+)-THIOMICAMINE	C27H29Br2NO5S
2,4-DIMETHYLBENZYLAMINE	C26H27Br2NO3
2-AMINOETHYL PHENYL SULFIDE	C25H25Br2NO3S
PHENETHYLAMINE	C25H25Br2NO3
TYRAMINE	C25H25Br2NO4
L-TYROSINE METHYL ESTER	C27H27Br2NO6
BENZHYDRYLAMINE	C30H27Br2NO3
4-METHOXYBENZYLAMINE	C25H25Br2NO4
2,3-DICHLOROBENZYLAMINE	C24H21Br2Cl2NO3
GLYCINE N-BUTYL ESTER HYDROCHLORIDE	C23H27Br2NO5
D-(-)-ALPHA-PHENYLGLYCINE ETHYL ESTER HYDROCHLORIDE	C27H27Br2NO5
4-CHLORO-2-FLUOROBENZYLAMINE HYDROCHLORIDE	C24H21Br2ClFNO3
TRANS-2-PHENYLCYCLOPROPYLAMINE HYDROCHLORIDE	C26H25Br2NO3
ETHYL 4-AMINOBUTYRATE HYDROCHLORIDE	C23H27Br2NO5
DL-HOMOCYSTEINE THIOLACTONE HYDROCHLORIDE	C21H21Br2NO4S
4-NITROBENZYLAMINE HYDROCHLORIDE	C24H22Br2N2O5
NORPHENYLEPHRINE HYDROCHLORIDE	C25H25Br2NO5
GLYCINE ETHYL ESTER HYDROCHLORIDE	C21H23Br2NO5
DL-ALANINE ETHYL ESTER HYDROCHLORIDE	C22H25Br2NO5
SARCOSINE ETHYL ESTER HYDROCHLORIDE	C22H25Br2NO5
4-NITRO-N-PROPYLBENZYLAMINE HYDROCHLORIDE	C27H28Br2N2O5
PIPERIDINE	C22H25Br2NO3
3-METHYLPIPERIDINE	C23H27Br2NO3
3-(HYDROXYMETHYL)-PIPERIDINE	C23H27Br2NO4
1,2,3,4-TETRAHYDROISOQUINOLINE	C26H25Br2NO3
2-ETHYLPIPERIDINE	C24H29Br2NO3
3,4-DICHLORO-N-ETHYLBENZYLAMINE	C26H25Br2Cl2NO3
2-METHYLPYRROLIDINE	C22H25Br2NO3
N-ETHYL-N-PROPYLAMINE	C22H27Br2NO3
4-METHYLPIPERIDINE	C23H27Br2NO3
(S)-(+)-2-(METHOXYMETHYL)PYRROLIDINE	C23H27Br2NO4
N-BENZYLETHANOLAMINE	C26H27Br2NO4
DIBENZYLAMINE	C31H29Br2NO3
4-BENZYL-4-HYDROXYPIPERIDINE	C29H31Br2NO4
(R)(-)-2-BENZYLAMINO-1-BUTANOL	C28H31Br2NO4
N-(N-ETHYLAMINOACETYL)-2,6-DIMETHYLANILINE	C29H32Br2N2O4
N-ETHYL-O-METHOXYBENZYLAMINE	C27H29Br2NO4
MAYBRIDGE NRB 01961	C30H33Br2NO5
2-((N-ETHYLAMINO)METHYL)-4-NITROPHENOL	C26H26Br2N2O6
MAYBRIDGE SEW 01484	C31H29Br2NO4S
3-AZABICYCLO-[3.2.2]NONANE	C25H29Br2NO3
N-(2-METHOXY-ETHYL)ETHYLAMINE	C22H27Br2NO4

18. The compound as defined in Claim 1 which is

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]valine,

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]leucine,

L-S-Benzyl, N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]cysteine,

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]tyrosine,

L-N-d-(2,2,5,7,8-Pentamethylchroman-6-sulfonyl),
N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]arginine,
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aminobutyric acid,
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]valine,
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]leucine,
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]proline,
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]cysteine,
N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]glycine,
L-N-a-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]lysine,
D-N-a-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]lysine,
N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]aminoisobutyric acid,
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]phenylglycine,
D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]phenylglycine,
N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]sarcosine,
DL-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]-a-methylphenylalanine,
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]isoleucine,
D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]methionine,
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]methionine,
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]phenylalanine,
D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]phenylalanine,
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]cyclohexylalanine,
L-N-e-(Benzyloxycarbonyl), N-a-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)-benzoyl]lysine,
D-N-e-(Benzyloxycarbonyl), N-a-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)-benzoyl]lysine,
D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]homoserine,
N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]glycine,
N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]sarcosine,
3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)phenylformylimino diacetic acid,
N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]-beta-alanine,
N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]-beta-alanine,
D-N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphennoxy)benzoyl]methionine.
L-N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]serine
D-N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]serine
N-[3,5-Dichloro-4-(4-hydroxy-3-bromophenoxy)benzoyl]glycine
N-[3,5-Dichloro-4-(4-hydroxy-3-methylphenoxy)benzoyl]glycine
N-[3,5-Dichloro-4-(4-hydroxy-3-ethylphenoxy)benzoyl]glycine

19. The compound as defined in Claim 1 which is

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]methionine,

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]methionine,

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl] a-methylalanine,

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspargine,

L-Methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]alanine,

L-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]alanine,

L-Dimethyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamate,

L-Dimethyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamate,

L-(O-*tert*-butyl)methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl] glutamate,

L-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamic acid,

L-N-[3,5-Dichloro-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartic acid,

D-di-*tert*-butyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamate,

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamic acid,

L-O-*tert*-Butyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamine,

L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamine,

D-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]glutamine,

L-O-Benzyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]aspartic acid,

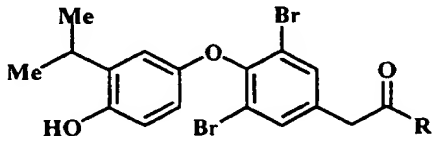
L-O-*tert*-Butyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]asparagine,

L-Methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]homoserine,

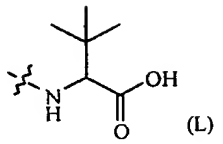
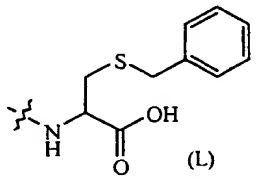
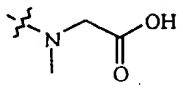
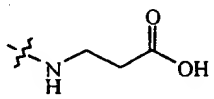
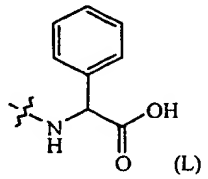
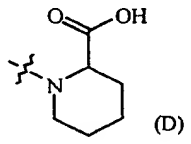
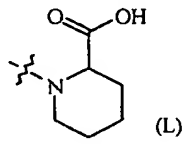
L-N-[3,5-Dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]homoserine,

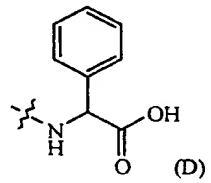
D-Methyl-N-[3,5-dibromo-4-(4-hydroxy-3-isopropylphenoxy)phenylacetyl]homoserine,

and the compounds showed in the table below,

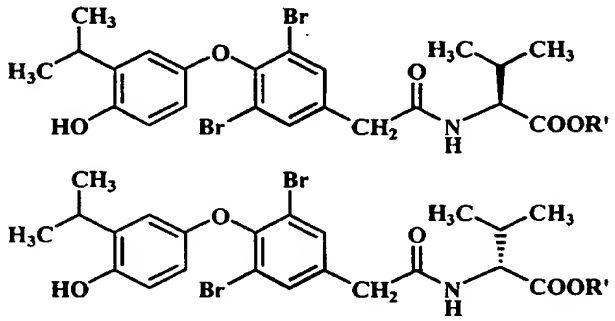


R	Mol Formel
L-Val	C22H25Br2NO5
L-Val	C22H25Br2NO5
L-Tyr	C26H25Br2NO6
	C23H27Br2NO5

 (L)	
 (L)	C27H27Br2NO5S
D-Leu	C23H27Br2NO5
D-Tyr	C26H25Br2NO6
D-Trp	C28H26Br2N2O5
L-Arg	C23H28Br2N4O5
L-Abu	C21H23Br2NO5
	C20H21Br2NO5
	C20H21Br2NO5
L-Leu	C23H27Br2NO5
 (L)	C25H23Br2NO5
D-Pro	C22H23Br2NO5
L-Ile	C23H27Br2NO5
 (D)	C23H25Br2NO5
L-Phe	C26H25Br2NO5
L-Lys	C23H28Br2N2O5
 (L)	C23H25Br2NO5
L-Pro	C22H23Br2NO5

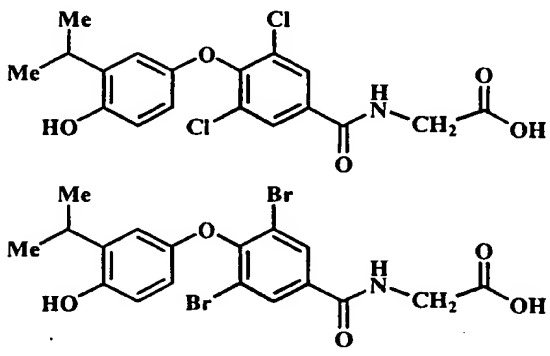
 (D)	C25H23Br2NO5

20. The compounds as defined in Claim 1 having the structures



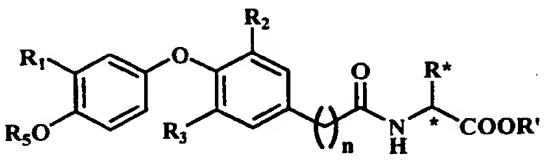
or a pharmaceutically acceptable salt or ester(s) thereof.

21. The compounds as defined in Claim 1 having the structures



or a pharmaceutically acceptable salt or ester(s) thereof.

22. The compounds as defined in Claim 1 having the structures



wherein R_1 = isopropyl, methyl, ethyl; R_2 and R_3 may be independently selected from Br, Cl and Me; n = 0 or 1; R* may be hydrogen, alkyl, cycloalkyl, aryl and heteroaryl; * denotes either D or L stereochemistry when R* is not hydrogen; R_5 is hydrogen; and R' is selected from hydrogen, lower alkyl, especially ethyl and methyl.

23. A method for preventing, inhibiting or treating a disease associated with metabolism dysfunction, or which is dependent on the expression of a T_3 regulated gene, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

24. The method as defined in Claim 23 wherein the disease associated with metabolism dysfunction or which is dependent on the expression of a T_3 regulated gene is obesity, hypercholesterolemia, atherosclerosis, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer, glaucoma, cardiac arrhythmia, congestive heart failure, or skin disorders.

25. The use of a compound according to Claim 1 in the preparation of a medicament for the treatment of a disease or disorders which is dependent on the expression of a T_3 regulated gene.

26. The use of a compound according to Claim 1 in which the disease or disorder is selected from hypothyroidism, hypercholesterolemia, obesity, skin disorders, glaucoma, cardiovascular disease, congestive heart failure and other endocrine disorders related to thyroid hormone.

27. A pharmaceutical composition comprising an effective amount of a compound according to Claim 1 or a pharmaceutically effective salt thereof, together with a pharmaceutically acceptable carrier.

28. The method according to Claim 24 in which the skin disorder or disease is dermal atrophy, post surgical bruising caused by laser resurfacing, keloids, stria, cellulite, roughened skin, actinic skin damage, lichen planus, ichtyosis, acne, psoriasis, Dernier's disease, eczema, atopic dermatitis, chloracne, pityriasis and skin scarring.

29. A method to treat skin disorder or disease by the use of a compound of Claim 1 in combination with a retinoid or a vitamin D analog.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 99/02084

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D257/04 C07C235/34 C07C323/59 C07D209/20 C07C279/14
C07D207/16 C07D211/60 C07C237/06 C07C235/52 A61K31/195
A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07C A61K C07B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US STN, CAPLUS accession no. 1971:540431, XP002139408 abstract; RN 33927-24-1, 34043-79-3 -& CHEMICAL ABSTRACTS, vol. 75, no. 23, 6 December 1971 (1971-12-06) Columbus, Ohio, US; abstract no. 140431, XP002139407 abstract & K. MASUDA ET AL: TAKEDA KENKYUSHO HO, vol. 29, no. 4, 1970, pages 545-552, --- -/--	1,2,5,6, 13,14, 23-27

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 June 2000	28/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Amsterdam, L

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 40048 A (KARO BIO AB) 19 December 1996 (1996-12-19) claims 1-14, 18-19, 21, 23-30, in particular claims 5, 25, 28: Triiodothyronamine	1,5,6, 14,23-29
X	DE 32 31 541 A (HENNING BERLIN GMBH) 1 March 1984 (1984-03-01) claims 1-3	1,5,6, 14,27
X	M. ANDRE ET AL: J. CHROMATOGR. A, vol. 725, no. 2, 1996, pages 287-294, XP004039616 page 293, figure 7, compound VI	1,2,5,6, 13,14
X	M. ADAMCZYK ET AL: BIOCONJUGATE CHEM., vol. 8, no. 2, 1997, pages 133-145, XP000906993 page 140, scheme 2, compounds 40, 41	1,2,5,6, 13,14
X	US 4 741 897 A (J. ANDREWS ET AL) 3 May 1988 (1988-05-03) examples 2-3	1,2,5,6, 13,14
A	EP 0 580 550 A (CIBA-GEIGY AG) 26 January 1994 (1994-01-26) page 6, lines 4-14; examples 1-15, 29-30	1,6,7, 10-12, 14,23-27
P,X	M. EBISAWA ET AL: CHEM. PHARM. BULL., vol. 47, no. 9, 1999, pages 1348-1350, XP000906992 figures 1 and 2, compounds 3b, 6b, 7b	1,5,6, 12-14, 23-27

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 99/02084

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 23-24 and 28-29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.